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An Advanced Treatise

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IN TWO VOLUMES

VOLUME I

SECOND EDITION



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SECOND EDITION

PREFACE TO THE SECOND EDITION

The purpose, plan, and scope of this treatise are given in the accompanying preface to the first edition.

This second edition, which represents a significant expansion of the first, contains twenty-six chapters, of which the following eight are new: the reactions of aliphatic hydrocarbons; synthetic polymers; catalytic hydrogenation and hydrogenolysis; organic sulfur compounds; aliphatic fluorides; the chemistry of the porphyrins; chlorophyll; and the redistribution reaction. All the chapters carried over from the first edition have been revised. In some chapters the literature has been reviewed up to September, 1942.

Corrections and suggestions will again be cordially welcomed. The editors are grateful to many friends for the examination of the manuscripts. Particular thanks are due to Messrs. R. K. Abbott, R. W. Leeper, D. S. Melstrom, G. J. O'Donnell, S. M. Spatz, J. R. Thirtle, and L. A. Woods.

H. G.

October, 1942

PREFACE TO THE FIRST EDITION

Organic chemistry is richly endowed with excellent textbooks. However, there is a need for a general treatise of organic chemistry suitable for instruction at the graduate level. Such a book must focus attention upon new developments. At best, it can but serve the purpose of the moment and provide a point of departure for unceasing revision.

The idea of a collaborative work by specialists in the several branches of the science was developed in 1934. Each author was asked to prepare a chapter dealing with a subject of particular interest to himself. It was hoped to obtain, in this way, an authoritative treatise which would cover most of the important phases of organic chemistry. The execution of this plan has resulted in the present volumes.

For the sake of convenience in revising and expanding the book, the rapidly developing fields of natural products, relationship between physical properties and chemical constitution, valence, and resonance have been grouped together in the second volume. It is planned to revise both volumes at intervals, not only in order to bring the present material up to date, but also to permit the inclusion of new chapters to fill the more conspicuous gaps. For example, chapters on polymerization and chlorophyll will be included in the next edition. Corrections and suggestions will be heartily welcomed.

The contents have been integrated and the accessibility of the information increased by cross references, by individual tables of contents for each chapter, and by a comprehensive subject index which is repeated in each of the two volumes. The inordinate wealth of the literature has made it necessary to restrict references, in general, to a relatively few selected original articles. Researches are cited, as a rule, by reference to the most recent publications; however, sufficient references to early work are given to provide an historical background. Occasional chapters, particularly those in the field of natural products, have abundant citations to original articles, and should be especially useful to research workers. In some chapters the literature has been reviewed up to September, 1937. There is, in addition, occasional mention of work hitherto unpublished. The section General References at the end of each chapter includes mention of some of the more important review articles and books as a guide to collateral reading.

The editors gratefully acknowledge the assistance of many friends in the examination of the manuscripts. Valuable aid was provided by the late Dr. W. H. Carothers, who served on the Editorial Board. Special thanks are due to Drs. G. E. Hilbert, J. F. Nelson, P. T. Parker, A. M. Patterson, G. F. Wright, and Messrs. J. C. Bailie, R. L. Bebb, L. C. Cheney, E. J. Crane, W. Harber, A. L. Jacoby, and J. Swislowsky.

H. G

December, 1937

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CHAPTER 1

THE REACTIONS OF ALIPHATIC HYDROCARBONS

GUSTAV EGLOFF

Universal Oil Products Company, Chicago

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I. ISOMERIZATION OF ALIPHATIC HYDROCARBONS

Aliphatic hydrocarbons are available in vast volumes from petroleum and natural gas. Isomerization of these hydrocarbons, although very difficult to control, is a most important reaction. Normal alkanes isomerize, in general, to methyl alkanes; the simplest case is the formation of isobutane, a key hydrocarbon in aviation gasoline, from *n*-butane via the alkylation process.

Isomerization of Alkanes. Normal alkanes isomerize to methyl-alkanes when treated with an aluminum halide.^{1, 2, 3, 4, 5} *n*-Butane in the presence of aluminum chloride and hydrogen chloride, in 4 hours at 175° and 35 atmospheres pressure, forms isobutane and lower alkanes.³ The equilibrium concentration of isobutane at 180° is 58 per cent.⁴ *n*-Butane and isobutane are slowly isomerized catalytically at room

¹ Montgomery, McAteer, and Franke, *J. Am. Chem. Soc.*, **59**, 1768 (1937).

² Montgomery, McAteer, and Franke, paper presented at Am. Chem. Soc. Meeting, Baltimore, April, 1939.

³ Ipatieff and Grosse, *Ind. Eng. Chem.*, **28**, 461 (1936).

⁴ Moldawsky and Nisovkina, *Compt. rend. acad. sci. U.R.S.S.*, **23**, 919 (1939) *J Gen. Chem. (U.S.S.R.)*, **9**, 1652 (1939).

⁵ Glasebrook, Phillips, and Lovell, *J. Am. Chem. Soc.*, **58**, 1944 (1936).

temperature. Both isomers require over 2 months to attain the equilibrium state in the presence of aluminum bromide at about 27° and 3 atmospheres pressure.¹ The equilibrium composition corresponds to over 78 per cent of isobutane; lower alkanes are formed in small amounts only.

Isopentane can be produced by isomerization of *n*-pentane in the presence of aluminum halides. It is a valuable volatile component of aviation fuels. The action of aluminum bromide upon *n*-pentane at room temperature yields 5 per cent of butanes (mostly isobutane), 55.9 per cent of isopentane, and 3.9 per cent of higher products.⁵ The equilibrium concentration of isopentane at 0° is 90 per cent.² At 80°, this value is decreased to 82 per cent.⁶ Hydrogen was used to suppress side reactions catalyzed by the aluminum chloride in the last case. A similar treatment of *n*-hexane at 80° resulted in the formation of 48 per cent of methylpentane, 12 per cent of dimethylbutane, and 7 per cent of side products. *n*-Hexane yielded 44 per cent of isohexanes at 120° for 2 hours with aluminum chloride.⁷ *n*-Hexane forms 2- and 3-methylpentanes.^{8,9} *n*-Heptane produces branched isomers, as shown in Table I.^{10,11} These data indicate that decompositions and recombinations accompany isomerizations in the presence of aluminum halides.

TABLE I
ISOMERIZATION OF *n*-HEPTANE BY AlCl₃ AT 96°

| Hydrocarbons Isolated | Parts of Hydro- carbons Isolated per 100 Parts of <i>n</i> -Heptane Reacted | Hydrocarbons Isolated | Parts of Hydro- carbons Isolated per 100 Parts of <i>n</i> -Heptane Reacted |
|----------------------------|--|--------------------------|--|
| Pentanes and lower alkanes | 64.6 | 3-Methylhexane | 1.6 |
| <i>n</i> -Hexane | 0.4 | 2,4-Dimethylpentane | 1.5 |
| 2-Methylpentane | 3.4 | 3,3-Dimethylpentane | 0.4 |
| 3-Methylpentane | 2.0 | 2,2,3-Trimethylbutane | 0.5 |
| <i>n</i> -Heptane | ... | Polymers | 24.4 |
| 2-Methylhexane | 1.2 | | |

The isomerization of only a few methylalkanes has been studied. 2-Methylpentane was isomerized to 3-methylpentane and 2,3-dimethyl-

⁶ Schmit, Hoog, and Verheus, *Rec. trav. chim.*, **59**, 793 (1940).

⁷ Bauer, "Über die katalytische Isomerisierung einiger Benzin-Kohlenwasserstoffe," Zürich, Deutsche Druckerei, Prague (1940).

⁸ McAteer, paper presented at Gibson Island Meeting of Am. Assoc. Adv. Science June 17-21, 1940.

⁹ Nenitzescu and Dragan, *Ber.*, **66**, 1892 (1933).

¹⁰ Calingaert and Beatty, *J. Am. Chem. Soc.*, **58**, 51 (1936).

¹¹ Calingaert and Flood, *ibid.*, **57**, 956 (1935).

butane or to a mixture of 2- and 3-methylpentanes by treatments with aluminum bromide and 96 per cent sulfuric acid, respectively.⁸ 3-Methylpentane gave considerable amounts of 2-methylpentane when subjected to either catalyst. The reported isomerizations of dimethylalkanes include interconversions of the 2,2- and 2,3-dimethylbutanes, with partial conversions to 2-methylpentane, upon contacting aluminum bromide at room temperature.

Isomerization of Alkenes. Normal alkenes isomerize by shifts of the double bond or the migration of a methyl group. 1-Butene yields 2-butene when treated thermally at 600–700°, or when treated catalytically at much lower temperatures with nickel and hydrogen, aluminum phosphate, aluminum sulfate, aqueous solutions of zinc chloride, benzenesulfonic acid, perchloric acid, or concentrated phosphoric acid.^{12, 13, 14, 15} 2-Butene isomerizes to 1-butene at 650–700° without catalysts or at 100° over phosphoric acid.^{12, 14} The 1- and 2-pentenes isomerize thermally.^{16, 17} 1-Hexene yields 2- and 3-hexenes and polymers upon treatment at 400° with molybdenum trisulfide and hydrogen under pressure.¹⁸

Several methods of isomerizing *n*-alkenes into isoalkenes have been used. *n*-Butenes isomerized to isobutene at 300–600° over activated silica-alumina, alumina, aluminum sulfate, or phosphoric acid.^{19, 20} At temperatures around 325°, 1-hexene yielded 2-methyl-2-pentene and iso-hexenes when catalyzed by zinc chloride and phosphoric acid, respectively.^{21, 22} The 1- and 2-octenes gave isoöctenes at 295–400° in experiments utilizing glass or quartz tubes, activated silica-alumina, phosphoric acid, or zinc chloride.^{21, 23, 24, 25}

Formation of isomers from methylalkenes, dimethylalkenes, and ethylalkenes has been studied to a greater extent than that of isomers from the corresponding alkanes. Among the methylalkene examples,

¹² Hurd and Goldsby, *ibid.*, **56**, 1812 (1934).

¹³ Twigg, *Trans. Faraday Soc.*, **35**, 934 (1939).

¹⁴ Ipatieff, Pines, and Schaad, *J. Am. Chem. Soc.*, **56**, 2696 (1934).

¹⁵ Gillet, *Bull. soc. chim. Belg.*, **29**, 192 (1920).

¹⁶ Hurd, *Ind. Eng. Chem.*, **26**, 50 (1934).

¹⁷ Hurd, Goodyear, and Goldsby, *J. Am. Chem. Soc.*, **58**, 235 (1936).

¹⁸ Petrov, Mescherjakov, and Andrejev, *Ber.*, **68**, 1 (1935); *J. Gen. Chem. (U.S.S.R.)*, **5**, 972 (1935).

¹⁹ Frost, Rudkovsky, and Serebriakova, *Compt. rend. acad. sci. U.R.S.S.*, **4**, 373 (1936).

²⁰ Serebriakova and Frost, *J. Gen. Chem. (U.S.S.R.)*, **7**, 122 (1937) [*C. A.*, **31**, 4569 (1937)].

²¹ Petrov and Cheltsova, *Compt. rend. acad. sci. U.R.S.S.*, **15**, 79 (1937).

²² Petrov and Shechukin, *J. Gen. Chem. (U.S.S.R.)*, **9**, 506 (1939) [*C.A.*, **33**, 9293 (1939)]

²³ Egloff, Morrell, Thomas, and Bloch, *J. Am. Chem. Soc.*, **61**, 3571 (1939).

²⁴ Hugel and Szayna, *Ann. combustibles liquides*, **1**, 781 (1926).

²⁵ Nemtsov, Nizovkina, and Soskina, *J. Gen. Chem. (U.S.S.R.)*, **8**, 1314 (1938).

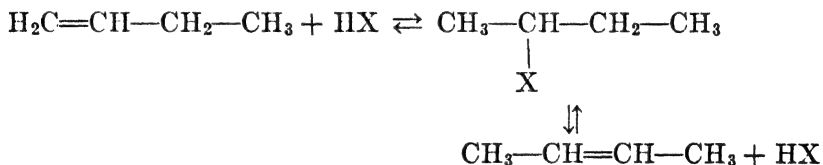
isobutene yielded *n*-butenes at 294° over phosphoric acid on "silicate."¹⁹ 3-Methyl-1-butene isomerized to 2-methyl-2-butene at 425–535° in the presence of alumina, aluminum sulfate, or phosphoric acid on pumice, while sulfuric acid effected a similar isomerization.^{26, 27} Aluminosilicates are more active in the isomerization of alkenes than aluminum oxide.²⁸

Isomerizations of the dimethylalkenes and ethylalkenes include an interconversion between 3,3-dimethyl-1-butene and a mixture of 2,3-dimethyl-1- and -2-butenes at 300° over phosphorus pentoxide on silica gel; the conversion of 3,3-dimethyl-1-butene to this mixture at 275° over aluminum sulfate; and the transformation of 3,7-dimethyl-1-octene into 3,7-dimethyl-2-octene over palladinized asbestos.^{29, 30}

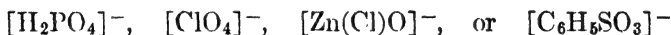
Other examples of isomerization among the alkenes include a partial conversion of *trans*-2-butene to the *cis*-form over phosphoric acid, and interconversion of the isomeric 2-pentenenes with the aid of ultra-violet light.^{14, 31, 32, 33, 34}

Formation of isomers from the alkenes must be accounted for by more than one mechanism since the isomerizations involve shifts of the double bond, methyl groups, or both. An acid-catalyzed double-bond shift is considered to consist of two steps:¹⁴ "(1) formation of an addition product of the alkene with the catalyst, and (2) the decomposition of the addition product from which the same olefin or one with a different structure is split off and the catalyst is regenerated."

The isomerization of 1-butene has been formulated as follows:



where "X" represents a group such as:



The removal of hydrogen from a more remote carbon atom is a supplemental mechanism, involving a short-lived cyclane, capable of explaining methyl group shifts or formation of any stable cyclanes:

²⁶ Ipatieff, *Ber.*, **36**, 2003 (1903); *J. Russ. Phys. Chem. Soc.*, **35**, 577 (1903).

²⁷ Norris and Reuter, *J. Am. Chem. Soc.*, **49**, 2624 (1927).

²⁸ Frost, *J. Phys. Chem. (U.S.S.R.)*, **14**, 1313 (1940).

²⁹ Laughlin, Nash, and Whitmore, *J. Am. Chem. Soc.*, **56**, 1395 (1934).

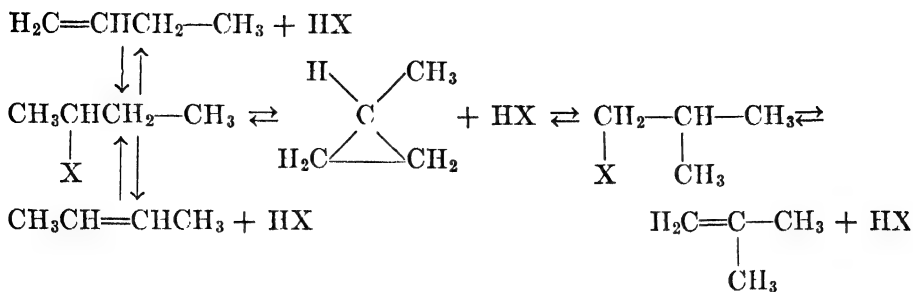
³⁰ Cramer and Glasebrook, *ibid.*, **61**, 230 (1939).

³¹ Sherrill, Baldwin, and Haas, *ibid.*, **51**, 3034 (1929).

³² Sherrill, Otto, and Pickett, *ibid.*, **51**, 3023 (1929).

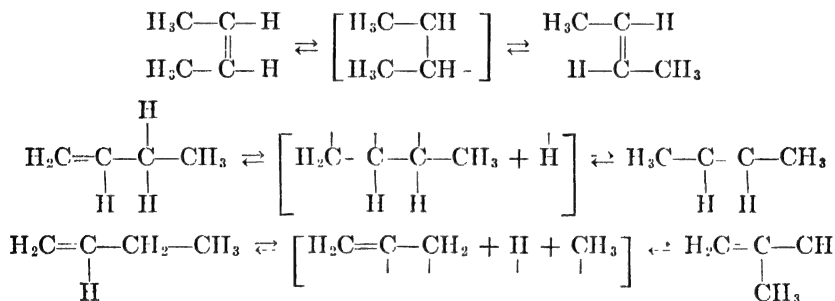
³³ Carr, *ibid.*, **51**, 3041 (1929).

³⁴ Kharasch, private communication to Sherrill, Otto, and Pickett, *J. Am. Chem. Soc.* **51**, 3023 (1929).



The conversion of a short-lived cyclane into its isomers may proceed also by an alternative thermal isomerization without HX.

Cis-trans isomerization, shifts of double bonds, and shifts of methyl groups may also be explained by free radical mechanisms:



Isomerization of Alkadienes. The allenic alkadienes isomerize to conjugated alkadienes or alkynes. Examples of the isomerization to conjugated alkadienes include treatment of 1,2-alkadienes with floridin at about 300° and with quinoline hydrobromide.^{35, 36, 37} 4,4-Dimethyl-1,2-pentadiene formed successively 2,4-dimethyl-1,3-pentadiene and 2,4-dimethyl-2,3-pentadiene over floridin at 230–235°; the formation of these products involves an interesting methyl group migration.³⁸ Instances wherein allenic alkadienes were converted into 1-alkynes are treatment with floridin at about 300° and isomerizations effected by potassium ethoxide solution at lower temperatures.^{35, 36, 39, 40} 1,2-Butadiene was converted into 2-butyne by hot potassium ethoxide solution.

The non-allenic alkadienes isomerize by (a) the shifting of double bonds and (b) cyclization in the presence of acidic catalysts. The following examples are known: 1,5-Hexadiene gave evidence of the for-

³⁵ Slobodin, *J. Gen. Chem. (U.S.S.R.)*, **5**, 48 (1935) [*C. A.*, **29**, 4732 (1935)].

³⁶ Slobodin, *ibid.*, **4**, 778 (1934) [*C. A.*, **29**, 2145 (1935)].

³⁷ Kutscherov, *J. Russ. Phys. Chem. Soc.*, **45**, 1634 (1913); *J. Chem. Soc.*, **104**, 1294 (1913).

³⁸ Slobodin, *J. Gen. Chem. (U.S.S.R.)*, **7**, 1664 (1937) [*C. A.*, **31**, 8501 (1937)].

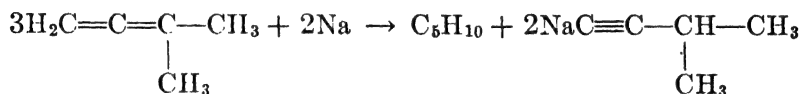
³⁹ Slobodin, *ibid.*, **6**, 1892 (1936) [*C. A.*, **31**, 4264 (1937)].

⁴⁰ Faworsky, *J. prakt. Chem.*, [2] **44**, 208 (1891).

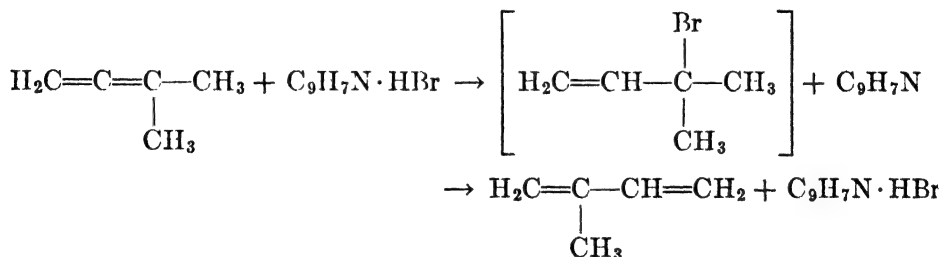
mation of 1,4- and 2,4-hexadiene when heated at 500° without catalyst or when treated at 170–360° with palladinized asbestos-carbon, alumina, chromia, floridin, or potassium ethoxide solution.^{16, 40, 41, 42, 43, 44, 45, 46} 2,4-Hexadiene yielded 1,3- and 1,4-hexadienes at 360–480° over alumina.⁴⁷ 2,5-Dimethyl-1,5-hexadiene formed 2,5-dimethyl-2,4-hexadiene at 180–225° in the presence of potassium ethoxide solution, floridin, or alumina.^{40, 44, 46}

2,6-Dimethyl-1,3-heptadiene was cyclized to 1,5,5-trimethyl-2-cyclohexene when treated with sulfuric acid.⁴⁸ 2,6-Dimethyl-2,6-octadiene isomerized to 1,5,5,6-tetramethyl-1-cyclohexene upon treatment with concentrated sulfuric acid, or with the same acid containing acetic acid.^{49, 50, 51}

In explanation of the mechanism of alkadiene isomerization, Faworsky recognized that a hydrogen disproportionation occurs in the conversion of 3-methyl-1,2-butadiene into a pentene and the sodium derivative of 3-methylbutyne:⁵²



According to Jozitsch, a butene resulted similarly during the formation of the sodium derivative of 1-butyne from 1,2-butadiene.⁴¹ The following equations illustrate the probable courses of two isomerizations effected by quinoline hydrobromide as catalyst:³⁷



⁴¹ Jozitsch, *J. Russ. Phys. Chem. Soc.*, **29**, 90 (1897) [*Chem. Zentr.*, I, 1011 (1897)].

⁴² Hurd and Bollmann, *J. Am. Chem. Soc.*, **55**, 699 (1933).

⁴³ Levina, *J. Gen. Chem. (U.S.S.R.)*, **6**, 1092 (1936) [*C. A.*, **31**, 1002 (1937)].

⁴⁴ Levina, *ibid.*, **7**, 1587 (1937) [*C. A.*, **31**, 8516 (1937)].

⁴⁵ Levina and Kiryushov, *ibid.*, **9**, 1834 (1939) [*C. A.*, **34**, 4051 (1940)].

⁴⁶ Lebedev and Slobodin, *ibid.*, **4**, 23 (1934) [*C. A.*, **28**, 5399 (1934)].

⁴⁷ Prévost, *Compt. rend.*, **208**, 1589 (1939).

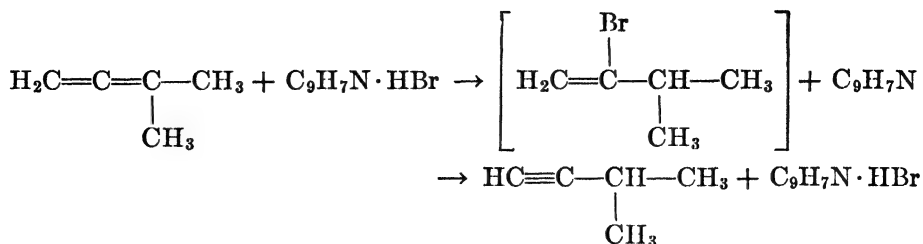
⁴⁸ Tiemann and Semmler, *Ber.*, **26**, 2708 (1893).

⁴⁹ Semmler, *Ber.*, **27**, 2520 (1894).

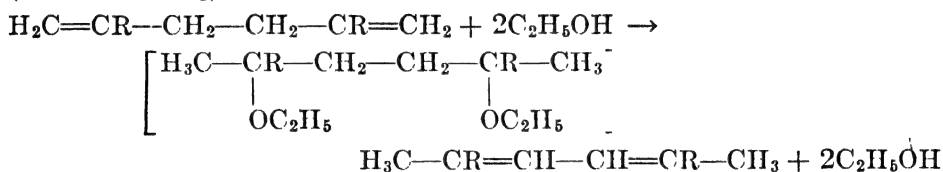
⁵⁰ Dupont, Dulou, and Desreux, *Bull. soc. chim.*, [5] **6**, 83 (1939).

⁵¹ Semmler, *Ber.*, **34**, 3122 (1901).

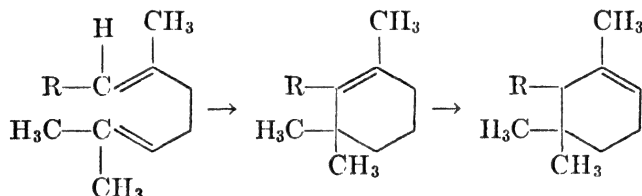
⁵² Faworsky, *J. prakt. Chem.*, [2] **37**, 417 (1888); *J. Russ. Phys. Chem. Soc.*, **19**, 555 (1887); *Ber.*, **21**, *Referate*, 177 (1888).



These resemble the conversion of a 1,5-alkadiene into a 2,4-alkadiene (R is H or CH₃):⁴⁰



Isomerization of alkadienes by cyclization in the presence of acidic catalysts may proceed as follows (R is H or CH₃):



Intermediary esters probably play a role in the postulated steps.

Isomerization of Alkapolynes. The alkapolynes isomerize by shifts of double bonds, conversion of two double bonds into a triple bond, and by cyclization or multicyclization. The following isomerizations are typical. 4,8-Dimethyl-1,3,7-nonatriene cyclized into 1,5-dimethyl-5-allyl-1-cyclohexene in the presence of 80 per cent sulfuric acid.⁵³ 2,6-Dimethyl-2,5,8-undecatriene formed 1,5,5-trimethyl-6-(1-butenyl)-1-cyclohexene when heated with sulfuric acid containing acetic acid.⁵⁴

Isomerization of Alkynes. A study of the data on isomerization of alkynes shows that a 1-alkyne will form a 1,2-alkadiene with the aid of potassium ethoxide solution, floridin, or heat alone; a 1,3-alkadiene in the presence of alumina or floridin; and a 2-alkyne by contact with potassium ethoxide solution, pumice, or soda-lime, or when heated alone.^{36, 39, 55, 56, 57} A 2-alkyne will form a 1-alkyne in the presence of sodium, sodamide, or floridin, but the last catalyst also yields a 1,2-alkadiene. Contact with sodamide transforms a 3-alkyne into a 1-alkyne.

⁵³ Grignard, *Ann. chim. phys.*, [7] **24**, 433 (1901).

⁵⁴ Kishner, *J. Russ. Phys. Chem. Soc.*, **43**, 1398 (1911) [*Chem Zentr.*, I, 1622 (1912)].

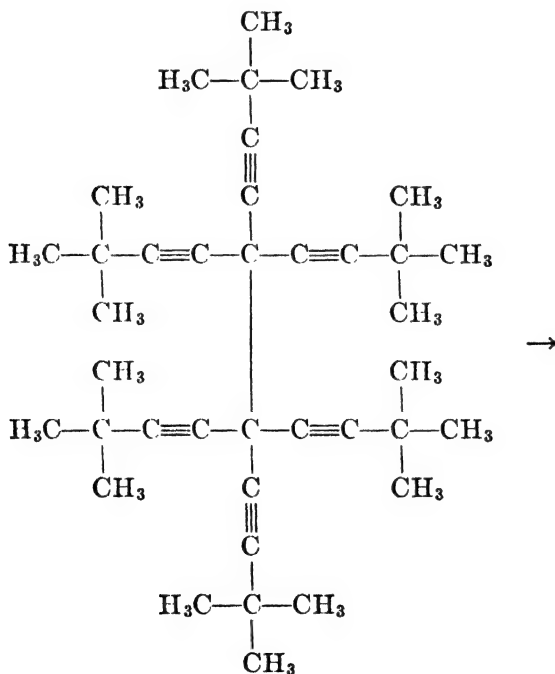
⁵⁵ Faworsky, *J. prakt. Chem.*, [2] **37**, 382 (1888).

⁵⁶ Faworsky, *J. Russ. Phys. Chem. Soc.*, **19**, 1, 414 (1887) [*Chem. Zentr.*, 1248 (1887)].

⁵⁷ Slobodin, *J. Gen. Chem. (U.S.S.R.)*, **7**, 2376 (1937) [*C. A.*, **32**, 2081 (1938)].

Heat is always used in isomerization of the alkynes. In the absence of catalysts, high temperatures are required. 1-Hexyne and 1-heptyne at 600° without catalysts were partly isomerized to the 1,2-alkadienes and a trace of the corresponding 2-alkynes.⁵⁸ 1-Alkynes or their corresponding sodium derivatives resulted when 2- and 3-heptynes, 2- and 3-octynes, and 2-nonyne were treated with sodamide at 160° or heated with sodium.^{52, 59, 60, 61, 62, 63}

Isomerization of Alkapolynes. 1,4-Hexadiyne isomerized to 2,4-hexadiyne when treated with potassium ethoxide solution.⁶⁴ The conversion of 1,5-hexadiyne into 2,4-hexadiyne is similar to that of 1,5-hexadiene into 2,4-hexadiene, wherein unsaturated bonds become conjugated through the agency of hot potassium ethoxide solution.⁴⁰ 2,2,9,9-Tetramethyl-5,5,6,6-tetra-*tert.*-butylethynyl-3,7-decadiyne gave 2,2,13,13-tetramethyl-5,10-di-*n*-butyl-7,8-di-*tert.*-butyl-tetradeca-5,6,8,9-tetraene-3,11-diyne when heated with alcohol or with xylene at 120–140°: ^{65, 66}



⁵⁸ Hurd and Christ, *J. Am. Chem. Soc.*, **59**, 2161 (1937).

⁵⁹ Guest, *ibid.*, **50**, 1744 (1928).

⁶⁰ Bourguet, *Ann. chim.*, [10] **3**, 325 (1925).

⁶¹ Behal, *Bull. soc. chim.*, [2] **50**, 629 (1888).

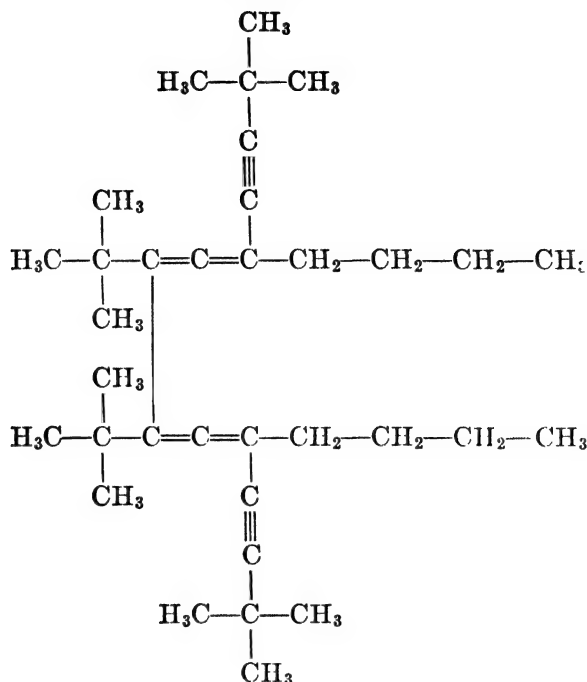
⁶² Desgrez, *Ann. chim. phys.*, [7] **3**, 209 (1894).

⁶³ Krafft and Reuter, *Ber.*, **25**, 2243 (1892).

⁶⁴ Lespieau, *Ann. chim.*, [9] **2**, 280 (1914).

⁶⁵ Sparks, Peppel, and Marvel, *J. Am. Chem. Soc.*, **59**, 1351 (1937).

⁶⁶ Salzberg and Marvel, *ibid.*, **50**, 1737 (1928).



The union of two rearranged free radicals is apparently responsible for isomer formation from the alkynyl hexasubstituted ethanes.

II. POLYMERIZATION OF UNSATURATED ALIPHATIC HYDROCARBONS

Polymerization of unsaturated aliphatic hydrocarbons has been the subject of much research during the past few years (see Chapter 8). Present-day investigations of polymerization are directed toward the mass production of polymers having predetermined molecular structures. The lower-molecular-weight polymers are utilized as high-octane-rating gasoline or as chemical intermediates. High polymers exhibit the properties of plasticity, elasticity, and lubricity, and in many ways resemble rubber and drying oils, all of which properties are of great value to science and industry.

"Polymerization has been defined as intermolecular combinations that are functionally capable of proceeding indefinitely (or leading to molecules of infinite size)." ^{67, 68} Polymerization may be divided into two types, the combination of identical molecules and the union of unlike molecules. The first type has been referred to as true, straight, and chain polymerization; the second as inter-, co-, cross, and mixed

⁶⁷ Carothers, *Chem. Rev.*, **8**, 354 (1931).

⁶⁸ Carothers, *Trans. Faraday Soc.*, **32**, 39 (1936).

polymerization. The term conjunct polymerization is applied to the reaction in which the formation of the product is effected by another type of reaction occurring either simultaneously with, preceding, or following the polymerization. Other terms used for this phenomenon are cyclo-, hydro-, and dehydropolymerization, which refer to polymerization accompanied by cyclization, hydrogenation, and dehydrogenation, respectively.

Generalizations on polymerization of hydrocarbons are given as follows:^{69, 70}

1. Hydrogen atoms on the unsaturated carbon-carbon linkage are necessary for polymerization. Some exceptions have been noted. For example, the product of dimerization of propadiene was 1,2-dimethylenecyclobutane, which indicates that the reaction began on the unhydrogenated atoms.⁷¹ The mechanism proposed is as follows: "It is considered that polymerization of two olefins proceeds primarily by the addition of a hydrogen atom and an unsaturated alkyl radical to a double bond. The double bond in the acceptor molecule is saturated by a hydrogen atom and an olefin radical supplied by the donor molecule. The active hydrogen atom in the donor molecule is taken as the one attached to a terminal carbon having a double bond or to that double-bonded carbon atom to which the smaller alkyl group is attached."

2. Polymerization tendencies decrease (with a few exceptions)⁷² as the molecular weight increases. When the double bond is in the terminal position of the molecule, its tendency toward polymerization is greatest, but when the double bond is shifted toward the center, the molecule acts more like an alkane.

Chain mechanisms propagated by free radicals or by activated molecules have been suggested as probable explanations for polymerization. Free radical propagation is illustrated by the following equation:



A polymerization supposedly of this type was initiated by the use of mercury vapor and light.⁷³ The polymerization stopped when illumination was removed. Chains of the free-radical type are broken by any means capable of terminating the free radical, particularly in this case

⁶⁹ Wachter, *Ind. Eng. Chem.*, **30**, 822 (1938).

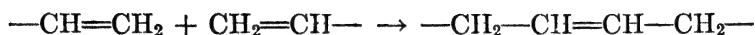
⁷⁰ Burk, *ibid.*, **30**, 1054 (1938).

⁷¹ Lebedev, *J. Russ. Phys. Chem. Soc.*, **45**, 1357 (1913) [*C. A.*, **9**, 799 (1915)].

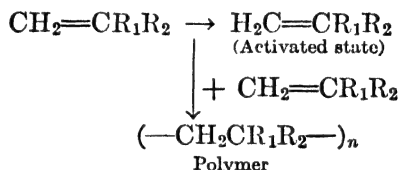
⁷² Ipatieff and Corson, *Ind. Eng. Chem.*, **27**, 1069 (1935).

⁷³ Melville, *Trans. Inst. Rubber Ind.*, **15**, 209 (1939); *Rubber Chem. Tech.*, **13**, 557 (1940).

by the interaction of two growing polymers. Parallel to this reaction, a "normal direct polymerization" propagated by activated molecules was carried out by illumination of the reactants. The activity continued after illumination ceased. Termination of this polymerization may be brought about by hydrogenation or addition of any substance capable of reaction with the double bond and by the reaction



in which the double bond is removed from the terminal position. Chain propagation by activated molecules may be represented by the equation ⁷⁴



Polymerization of Alkenes. Alkenes undergo polymerization at moderately high temperatures, but decomposition and isomerization are competing reactions.⁷⁵ Thermal polymerization of ethene at 330° and 64 atmospheres resulted in the formation of polymeric alkanes, alkenes, and cyclic products.⁷⁶ In the polymerization of ethene, addition of 0.02 per cent oxygen was found to double the yield over that obtained in the absence of oxygen.⁷⁷ Elevated temperatures were undesirable in the polymerization of ethene since decomposition began around 525° and at 570° the pyrolysis products, hydrogen, methane, and ethane, were found.⁷⁸

In the presence of catalysts, alkenes polymerize without undesirable side reactions. Proper choice of catalyst and reaction conditions makes possible the formation of polymers with specific properties. For example, high-octane gasoline has been obtained from the simultaneous polymerization and hydrogenation of isobutene in the presence of phosphoric acid-nickel oxide-iron catalyst.⁷⁹ Alkene polymerizations have been carried out with catalysts such as alumina on silica,⁸⁰ boron trifluo-

⁷⁴ Chalmers, *Can. J. Research*, **7**, 113 (1932).

⁷⁵ Egloff, "Reactions of Pure Hydrocarbons," Reinhold Publishing Corp., New York (1937), p. 243.

⁷⁶ Ipatieff and Pines, *Ind. Eng. Chem.*, **27**, 1364 (1935).

⁷⁷ Storch, *J. Am. Chem. Soc.*, **56**, 374 (1934).

⁷⁸ Pease, *ibid.*, **52**, 1158 (1930).

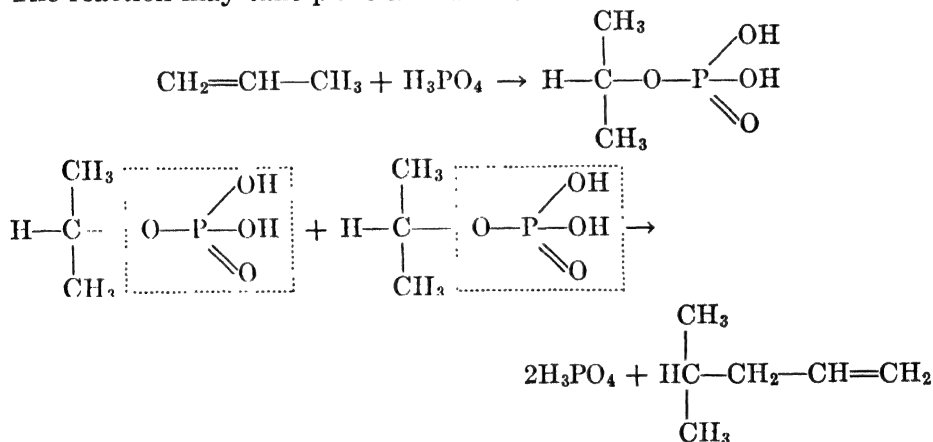
⁷⁹ Ipatieff and Komarewsky, *Ind. Eng. Chem.*, **29**, 958 (1937)

⁸⁰ Gayzer, *ibid.*, **25**, 1122 (1933).

ride,^{81, 82} chlorides of aluminum,^{83, 84} magnesium,⁸⁵ and zinc,⁸³ phosphorus pentoxide,⁸⁶ and phosphoric^{87, 88} and sulfuric acids.^{89, 90} Polymerization of propene over alumina, alumina on silica, or floridin resulted in the formation of liquid alkenes of five to nine carbon atoms and some alkanes.⁸⁰

Alkene polymerization using aluminum chloride may involve cyclization and hydrogen disproportionation. In the polymerization of ethene with aluminum chloride, hydrogenation, dehydrogenation, and cyclization occur to such an extent that the products consist of alkanes and cyclenes.⁹¹ The presence of traces of water vapor or hydrogen chloride was necessary for polymerization of ethene with pure aluminum chloride as catalyst. The products from ethene with anhydrous aluminum chloride at 180° were liquid hydrocarbons and an aluminum chloride complex which indicates that the mechanism of polymerization is similar to that of the Friedel-Crafts reaction.⁸⁴

Polymerization of propene and butenes in the presence of 100 per cent orthophosphoric acid has been shown to take place through intermediate ester formation with subsequent regeneration of the acid.⁹² The reaction may take place as indicated:



⁸¹ Ruthruff, "Action of Boron Halides on Hydrocarbons," paper presented at Am. Chem. Soc. Meeting, Boston, September, 1939.

⁸² Otto, *Brennstoff-Chem.*, **8**, 321 (1927).

⁸³ Ipatieff and Rutala, *Ber.*, **46**, 1748 (1913).

⁸⁴ Stanley, *J. Soc. Chem. Ind.*, **49**, 349T (1930).

⁸⁵ Burk, "Catalysis and Polymerization," paper

ing. Baltimore, 1939.

⁸⁶ Malishev, *Ogl-Kohle Erdoel Teer*, **14**, No. 23, 479 (1938).

⁸⁷ Ipatieff and Schaad, *Ind. Eng. Chem.*, **30**, 596 (1938).

⁸⁸ Ipatieff and Corson, *ibid.*, **27**, 1069 (1935).

⁸⁹ Ormandy and Craven, *J. Inst. Petroleum Tech.*, **13**, 844 (1927).

⁹⁰ Ormandy and Craven, *J. Soc. Chem. Ind.*, **47**, 317T (1928).

⁹¹ Ipatieff and Grosse, *J. Am. Chem. Soc.*, **58**, 915 (1936).

⁹² Ipatieff, *Ind. Eng. Chem.*, **27**, 1067 (1935).

From the evidence obtainable, it seems that asymmetrical substitutions favor dimerization and other polymerization reactions, although the supporting data are derived essentially from the aromatic rather than the aliphatic series.⁹³ The dimerizing agent is usually an acid such as phosphoric or sulfuric and the reaction may momentarily involve the addition of a proton.⁹⁴ When the proton is added, changes take place which are characteristic of an atom deficient in electrons; polymerization is one of these.

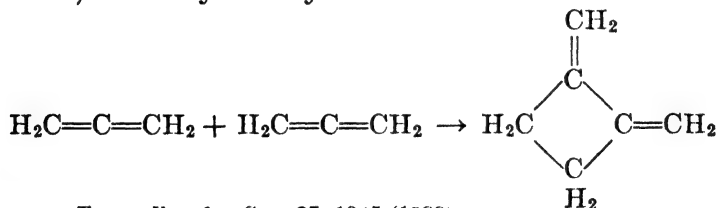
Alkene polymerizations carried out in the presence of sulfuric acid may form alkanes, alkenes, and cyclic hydrocarbons.^{89, 90} In addition to dimeric polymers, higher polymers were produced from isobutene in contact with more concentrated acid.^{95, 96, 97} As with phosphoric acid, sulfuric acid-catalyzed polymerization of alkenes involves the formation and decomposition of intermediate esters.⁹⁸

Polymers of ethene have been produced by the ozonizer, semi-corona, and the electrodeless discharge.⁹⁹ Reactions carried out in the ozonizer gave dimers and trimers of propene, 2-butene, and isobutene. Dehydrogenation was the primary reaction with the subsequent formation of heavy liquid polymers.

Polymerization of Alkadienes. Lebedev in discussing polymerization of allenes gave the following principles concerned with that reaction:¹⁰⁰

1. Allenes "polymerize much more readily than the divinyls."
2. "In the polymerization of allenes the union of molecules takes place at the central carbon atoms, these being the least saturated. This gives rise to both cyclic and spiral arrangements."

The more highly unsaturated carbon atoms are the first to react in the formation of cyclic products from allenic molecules; thus propadiene dimerizes to 1,2-dimethylenecyclobutane:⁷¹



⁹³ Bergmann, *Trans. Faraday Soc.*, **35**, 1025 (1939).

⁹⁴ Whitmore, *Ind. Eng. Chem.*, **26**, 94 (1934).

⁹⁵ Lebedev and Kobliansky, *Ber.*, **63B**, 103 (1930).

⁹⁶ McCubbin, *J. Am. Chem. Soc.*, **53**, 356 (1931).

⁹⁷ Ipatieff and Pines, *J. Org. Chem.*, **1**, 464 (1936).

⁹⁸ Ipatieff, "Catalytic Reactions at High Pressures and Temperatures," Macmillan Co., New York (1936), p. 549.

⁹⁹ Thomas, Egloff, and Morrell, *Chem. Rev.*, **28**, 1 (1941).

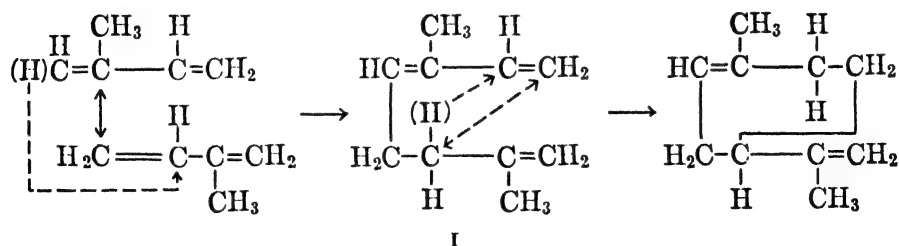
¹⁰⁰ Lebedev and Mereshkovskii, *J. Russ. Phys. Chem. Soc.*, **45**, 1249 (1913) [*C. A.*, **8**, 320 (1914)].

Thermal polymerization at 270° of the non-conjugated 1,4-pentadiene results in the formation of 1-methyl-2-propenylcyclohexene.¹⁰¹ This product is probably formed as a result of isomerization preceding dimerization, but the possibility of initial formation of the dimeric free radical, $\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}-\text{CH}_2-\text{CH}=\text{CH}_2$, may not be entirely eliminated.¹⁰²

Alkadienes having substituents on the non-terminal carbons of the group $\text{C}=\text{C}-\text{C}=\text{C}$ polymerize more readily than those in which the terminal carbons of the conjugated group are substituted. The rate of polymerization is also increased where ring formation occurs in the chain containing the conjugated system. At 750°, 2-methyl-1,3-pentadiene formed a series of aromatics.¹⁰³ The conjugated alkadiene, 2,4-hexadiene, polymerized readily at temperatures between 100° and 150°.¹⁰⁰

Catalytic polymerization of alkadienes is brought about by various substances, especially the alkali and alkaline-earth metals. The organo-metallic derivatives of the alkali metals catalyze condensation of alkadienes to unsaturated polymers, saturated polymers, and both alicyclic and aromatic compounds. Catalytic polymerization products of a cyclic nature have been obtained as the dimeric forms. In this case, the conjugated dienes exhibit a combination of 1,2- and 1,4-addition which produces alkenylcyclohexenes.⁹³

Alkali and alkaline-earth metals have been used to catalyze alkadiene polymerizations. With metallic sodium, butadienes gave high aliphatic polymers.¹⁰⁴ A series of arrested dimerizations catalyzed by potassium in alcohol, however, produced cyclic dimers and indicated that the ring closures occurred in the following stages:¹⁰⁵



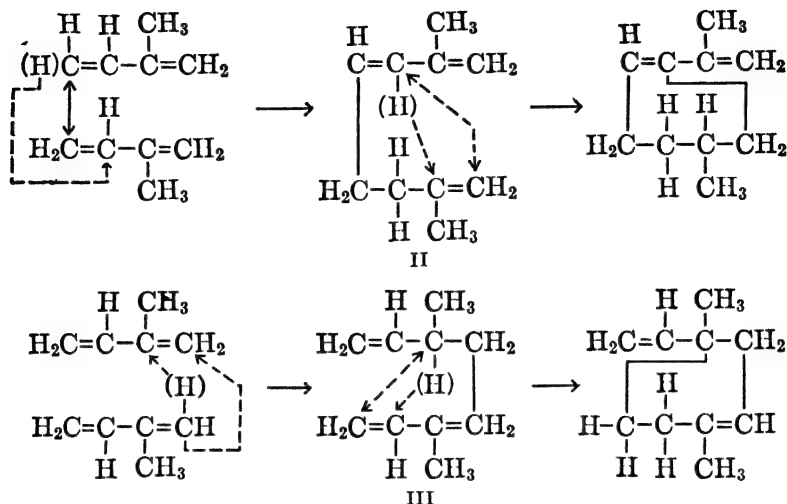
¹⁰¹ Farmer, *Trans. Faraday Soc.*, **35**, 1034 (1939).

¹⁰² Ahmad and Farmer, *J. Chem. Soc.*, 1176 (1940).

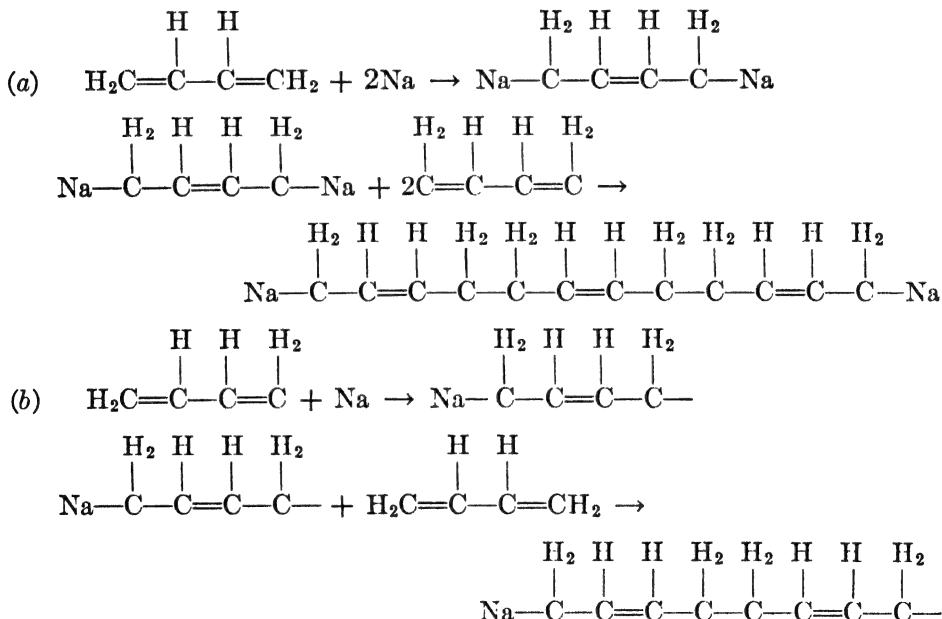
¹⁰³ Staudinger, Endle, and Herold, *Ber.*, **46**, 2466 (1913).

¹⁰⁴ L'vov, *J. Gen. Chem. (U.S.S.R.)*, **7**, 928 (1937) [*C. A.*, **31**, 5318 (1937)].

¹⁰⁵ Sparks, Rosen, and Frolich, *Trans. Faraday Soc.*, **35**, 1040 (1939).



Probable mechanisms of polymerization in the presence of alkali metals are (a) the formation of addition compounds with the alkali metal¹⁰⁶ and (b) free-radical chains.¹⁰⁷



Condensations of 1,3-butadiene and 2-methyl-1,3-butadiene have been carried out in the presence of phenylisopropylpotassium.^{108, 109}

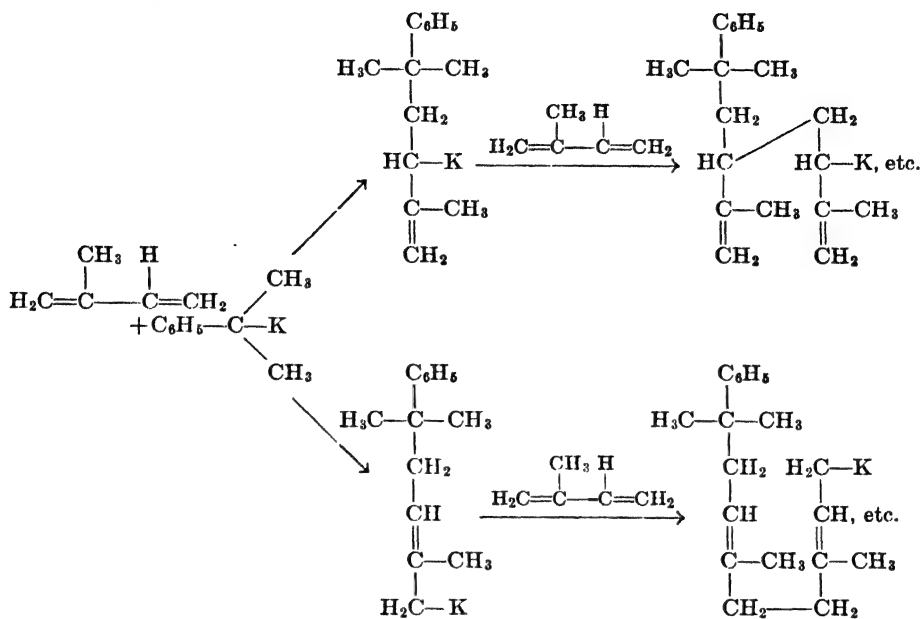
¹⁰⁶ Abkin and Medvedev, *ibid.*, **32**, 286 (1936).

¹⁰⁷ Bergmann, *ibid.*, **32**, 295 (1936).

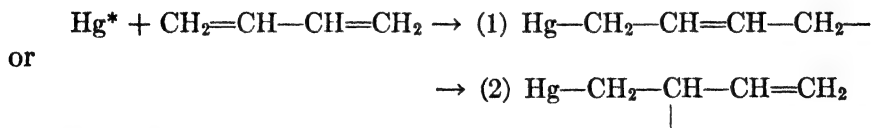
¹⁰⁸ Ziegler and Kleiner, *Ann.*, **473**, 57 (1929).

¹⁰⁹ Ziegler, Dersch, and Wollthan, *Ann.*, **511**, 13 (1934).

The stepwise reaction probably involves 1,2- or 1,4-addition of the potassium and the phenylisopropyl group:



Titanium chloride in chloroform and stannic chloride catalyzed the formation of cyclic polymers from 2-methyl-1,3-butadiene.¹¹⁰ The addition of oxygen to 2,3-dimethyl-1,3-butadiene catalyzed polymerization resulting, possibly, from the formation of peroxides.¹¹¹ Acetic acid with sulfuric acid promoted the polymerization of 2-methyl-1,3-butadiene into terpenes.¹¹⁰ Butadiene polymerized in the presence of mercury vapor as a result of photosensitization.¹¹² The yield as shown by the number of molecules polymerized per quantum of light was independent of temperature and pressure. Chains are apparently initiated by the sensitized mercury atoms with the reaction proceeding as follows:



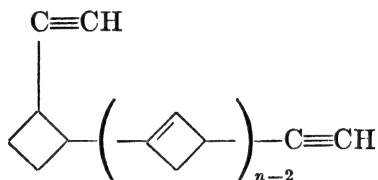
Formation of (1) predominates over (2). The reaction occurs partially at the surface with both deactivation and activation of polymers taking place at the surface.

¹¹⁰ Wagner-Jauregg, *Ann.*, **496**, 52 (1932).

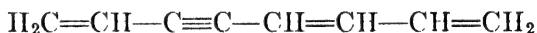
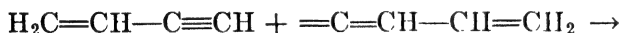
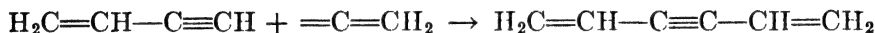
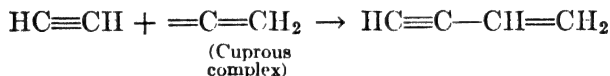
¹¹¹ Staudinger and Lautenschläger, *Ann.*, **488**, 1 (1931).

¹¹² Gee, *Trans. Faraday Soc.*, **34**, 712 (1938).

Polymerization of Alkynes. Thermal polymerization of ethyne to benzene and other aromatic hydrocarbons has been known for many years.¹¹³ Between 300° and 500° thermal polymerization of ethyne occurs without excessive decomposition of the hydrocarbon.¹¹⁴ At the beginning of the polymerization, there is apparently a bimolecular, homogeneous reaction.^{115, 116} Evidence indicates, however, that in later stages polymerization is a unimolecular process. Both aliphatic and aromatic compounds may be obtained from catalyzed alkyne polymerizations.¹¹⁷ It is postulated that the polymers of ethyne contain cyclic structures (n = number of molecules of but-1-en-3-yne):¹¹⁸



Aliphatic compounds were obtained from ethyne in the presence of cuprous chloride, ammonium chloride, metallic copper, and moisture.¹¹⁹ The reaction probably involves the formation of complex cuprous salts of ethyne:



Cyclic polymers are formed from ethyne when it is heated in the presence of acids, acid anhydrides, or phenols.¹¹⁸ By using an electric discharge, polymerization of alkynes to alkadiynes and alkadienyne was effected.¹²⁰ Photopolymerization gave both aliphatic and aromatic polymers.^{121, 122, 123}

¹¹³ Berthelot, *Bull. soc. chim.*, [2] **11**, 4 (1869).

¹¹⁴ Schläpfer and Brunner, *Helv. Chim. Acta*, **13**, 1125 (1930).

¹¹⁵ Pease, *J. Am. Chem. Soc.*, **51**, 3470 (1929).

¹¹⁶ Taylor and Van Hook, *J. Phys. Chem.*, **39**, 811 (1935).

¹¹⁷ Kato and Aikawa, *J. Elektrochem. Assoc. Japan*, **3**, 261 (1935) [*C. A.*, **30**, 2555 (1936)]; Iki and Ogura, *J. Soc. Chem. Ind. Japan*, **30**, 461 (1927) [*C. A.*, **21**, 3046 (1927)].

¹¹⁸ Dykstra, *J. Am. Chem. Soc.*, **56**, 1625 (1934).

¹¹⁹ Nieuwland, Calcott, Downing, and Carter, *ibid.*, **53**, 4197 (1931).

¹²⁰ de Saint-Aunay, *Chimie & industrie*, **29**, 1011 (1933).

¹²¹ Lind and Livingston, *J. Am. Chem. Soc.*, **54**, 94 (1932).

¹²² Kemula and Mrazek, *Z. physik. Chem.*, **23B**, 358 (1933).

¹²³ Livingston and Schifflett, *J. Phys. Chem.*, **38**, 377 (1934).

Ethyne polymerizes when subjected to the α -rays from radon.¹²⁴ A mercury photosensitized reaction at temperatures up to 500° gave ethyne polymers containing 200 carbon atoms.¹²⁵ The rate of reaction was independent of the ethyne pressure but was proportional to the rate of chain initiation, which depends upon light intensity. The chain reaction involving a complex activated mercury-ethyne combination may be stopped by a "collision between an ethyne molecule and the polymer, of a different character to the propagating collision."

Ethyne also combines with alkenes to form unsaturated hydrocarbons of higher molecular weight.¹²⁶ Although thermal polymerization of an alkyne and alkene at higher temperatures yields alkadienes, thermal polymerization at lower temperatures and catalytic polymerization yield alkynes of higher molecular weight.^{127, 128} The alkadiene probably results from isomerization at the higher temperatures.

III. ALKYLATION OF ALKANES

One of the most important processes in hydrocarbon chemistry is the alkylation of an alkane with an alkene. The reaction of isobutane with alkenes, discovered by Ipatieff, was the beginning of many studies resulting in the commercial use of this fundamental reaction. The alkylation of aliphatic hydrocarbons is an important reaction in the commercial production of aviation gasoline. Alkylation is the basis for producing neohexane (2,2-dimethylbutane) from isobutane and ethene, or 2,2,4-trimethylpentane from isobutane and isobutene, now commercial processes for preparing aviation gasoline.

Alkylation of aliphatic hydrocarbons may be defined broadly as the replacement of hydrogen atoms of an alkane by alkyl groups. Polymerization of alkenes can be considered as alkylation. These reactions are discussed separately under "Polymerization."

Isoalkanes are readily alkylated at or above room temperature when boron trifluoride, nickel, and hydrogen fluoride are used together as the catalyst.¹²⁹ From the reactions of isobutane, 2-methylbutane, and 2,2,4-trimethylpentane with ethene, and isobutane with isobutene, a series of isoalkanes containing even and odd numbers of carbon atoms per molecule is always obtained. The cracking reaction accompanies the alkylations.

¹²⁴ Mund, Velghe, Devos, and Vanpee, *Bull. soc. chim. Belg.*, **48**, 269 (1939) [*C. A.*, **33**, 9145 (1939)]

¹²⁵ Melville, *Trans. Faraday Soc.*, **32**, 258 (1938).

¹²⁶ Berthelot, *Bull. soc. chim.*, [2] **6**, 268 (1866).

¹²⁷ Prunier, *Ann. chim. phys.*, [5] **17**, 16 (1879).

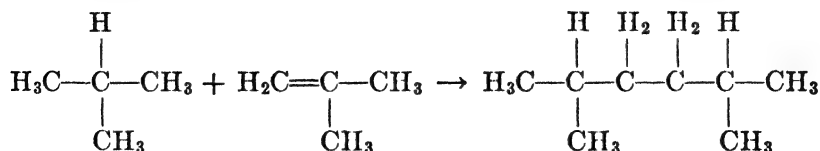
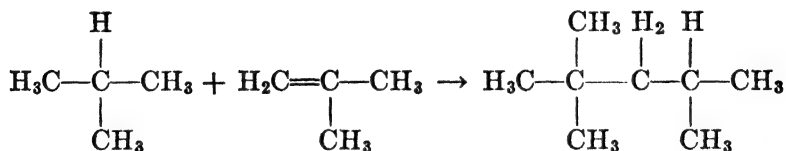
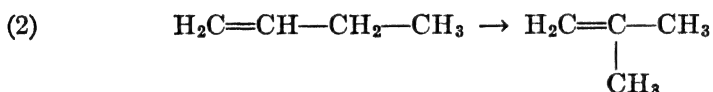
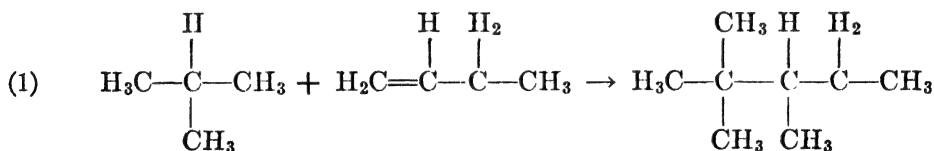
¹²⁸ Dubose and Luttringer, "Rubber," C. Griffin and Co., Ltd., London (1918), p. 253.

¹²⁹ Ipatieff and Grosse, *J. Am. Chem. Soc.*, **57**, 1616 (1935).

The abnormal behavior of 2,2,4-trimethylpentane under ethylation can be ascribed to a dealkylation into isobutane and isobutene. The boron trifluoride apparently acts by formation of complexes with the alkane. The action of aluminum chloride on *n*-butane, *n*-hexane, *n*-heptane, and 2,2,4-trimethylpentane has been assumed to be a splitting of the original hydrocarbon into a smaller alkane and an alkene which immediately alkylates other alkane molecules present.³

Further investigations of alkylation have shown that the reaction is a general one for higher alkanes.¹³⁰ The alkylations of isobutane and *n*-hexane with ethene were catalyzed by aluminum chloride at about 15 atmospheres pressure.^{130, 131} The products were alkanes up to dodecanes from isobutane and higher-molecular-weight products from *n*-hexane.

Alkylation using aluminum chloride at low temperatures and atmospheric pressure produced a monoalkylation.¹³² Very low temperatures (-100°) were undesirable, since inactivity of the alkanes caused polymerization of alkenes to predominate over the alkylation reaction. Alkylation of isobutane with a mixture of 1- and 2-butenes at -35° yielded isoöctanes and isododecanes in a 5 : 1 proportion. The isoöctanes are made up largely of 2,2,3- and 2,2,4-trimethylpentane, which indicates that some isomerization of the *n*-butenes to isobutene took place. These reactions are illustrated as follows:



¹³⁰ Ipatieff, Grosse, Pines, and Komarewsky, *ibid.*, **58**, 913 (1936).

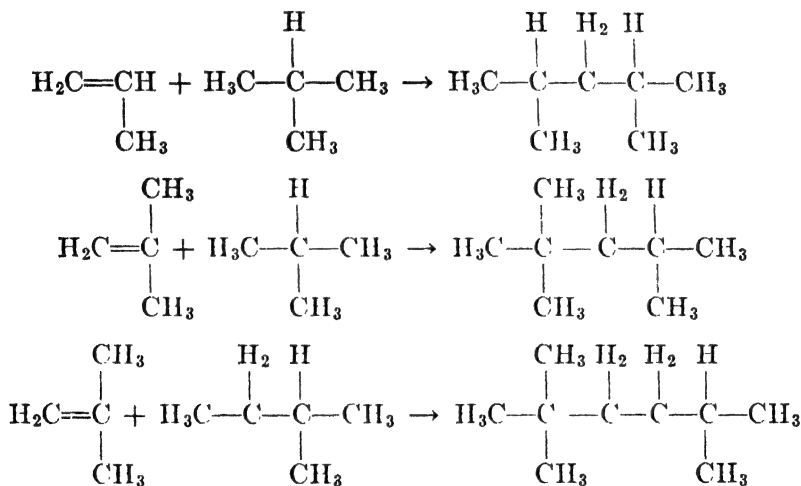
¹³¹ Ipatieff, "Catalytic Reactions at High Pressures and Temperatures," Macmillan Co., New York (1936), p. 673.

¹³² Pines, Grosse, and Ipatieff, *J. Am. Chem. Soc.*, **64**, 33 (1942).

Catalysts less active than aluminum chloride can be used to advantage at higher temperatures. Isobutane and ethene reacted at 100° in the presence of zirconium chloride, yielding 99 per cent of alkanes.^{133, 134}

Several investigators have described alkylations of isoalkanes by alkenes in the presence of concentrated sulfuric acid at ordinary temperatures. The use of too highly concentrated acids leads to carbonization, oxidation of hydrocarbons, and a decrease in the octane rating and yield of the alkylate. An excess of isoalkane over that required for equimolecular addition to the alkene results in an increased yield of aviation gasoline and in a decreased amount of high-boiling hydrocarbons. Evidently, such excess of isoalkane prevents or reduces polymerization of the alkenes. Highly branched alkanes were formed from isobutane by addition of the following alkenes in the presence of sulfuric acid: 1-butene, 2-butene, isobutene, and 2-methyl-2-butene.

Alkylations in the presence of sulfuric acid proceed by the union of an alkyl group containing a primary carbon atom with an unsaturated group containing a tertiary or quaternary carbon atom:¹³⁵



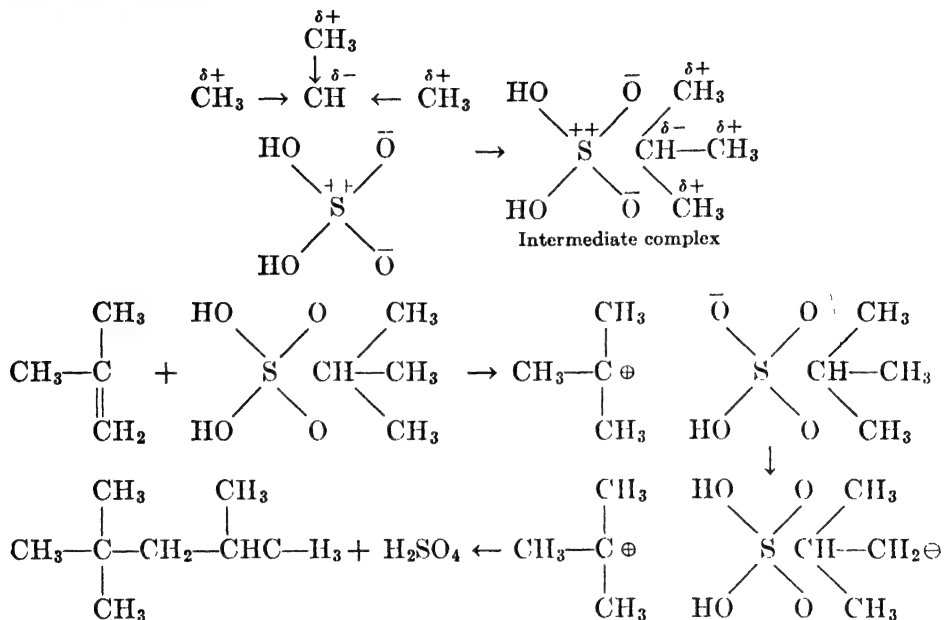
Alkylations of isoalkanes by alkenes are assumed to involve: (1) the formation of an intermediate complex between the isoalkane and sulfuric acid; (2) the transfer of a proton from the sulfuric acid to an alkene, whereby the last molecule forms a positive or carbonium fragment; (3) the restoration of the issuing hydrogen sulfate part by the transfer of a proton from a terminal methyl group of the attached isoalkane,

¹³³ Ipatieff, "Catalytic Reactions at High Pressures and Temperatures," Macmillan Co., New York (1936), p. 682.

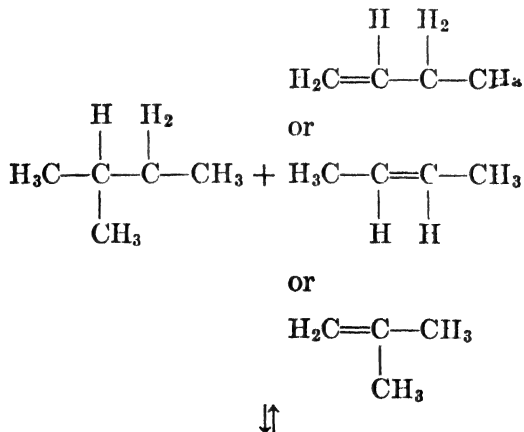
¹³⁴ Ipatieff, Grosse, and Komarewsky, paper presented at Am. Chem. Soc. Meeting, San Francisco, 1935.

¹³⁵ Birch, Dunstan, Fidler, Pim, and Tait, *Ind. Eng. Chem.*, **31**, 1079 (1939).

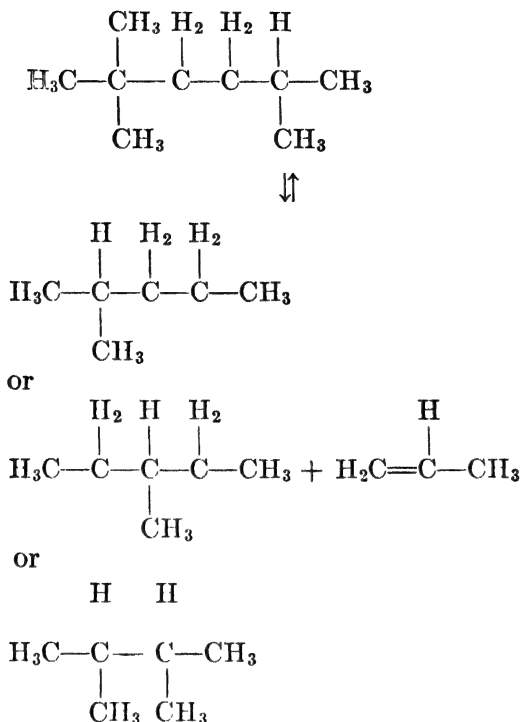
making the latter a carbanion; and (4) the union of carbanion and carbonium ion with liberation of free sulfuric acid.¹³⁶ These steps are patterned after the mechanism for an acid-catalyzed polymerization, and are illustrated as follows:



The foregoing representations, however, are attended both by the general difficulties of the carbonium-ion theory and by disregard of dehydrogenation-hydrogenation and other reactions occurring in the presence of sulfuric acid. Numerous secondary reactions accompany an alkylation catalyzed by sulfuric acid. For example, the butene and methylbutane reaction may proceed as indicated:



¹³⁶ Birch and Dunstan, *Trans. Faraday Soc.*, **35**, 1013 (1939).



One observation seriously contradicts the carbonium-ion theory of alkylation, namely, the formation of typical alkylates at -12° by slow addition of diisopropyl sulfate to a mixture of isobutane and sulfuric acid.¹³⁵

The foregoing examples of alkylation of alkanes, using boron trifluoride, aluminum chloride, zirconium tetrachloride, or sulfuric acid as catalysts, present the well-defined catalytic procedures. Other alkylation processes are either of thermal nature or of more complicated catalytic character.

Neohexane (2,2-dimethylbutane) is produced commercially by the thermal process and marketed as a high-volatility aviation fuel.¹³⁷

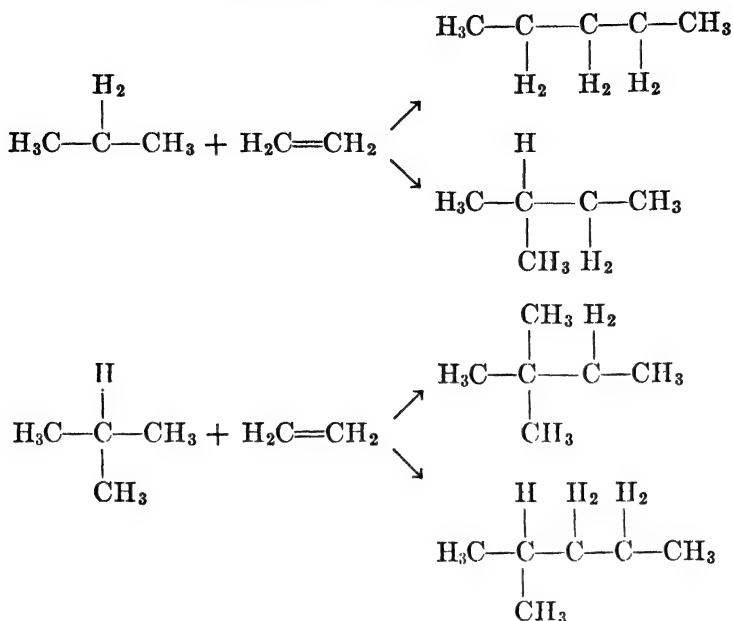
Propane has been alkylated by ethene at temperatures about 500° and over 300 atmospheres pressure, yielding *n*- and isopentanes. A similar treatment of isobutane and ethene gave 2,2-dimethylbutane and 2-methylpentane.^{138, 139, 140} These thermal alkylations proceed without isomerization:

¹³⁷ Oberfell and Frey, *Natl. Petroleum News*, **31**, No. 48, R-502 (1939); *Oil Gas J.*, **38**, No. 29, 70 (1939).

¹³⁸ Frey and Hepp, *Ind. Eng. Chem.*, **28**, 1439 (1936).

¹³⁹ Frey, *Oil Gas J.*, **35**, No. 34, 40 (1937).

¹⁴⁰ Oberfell and Frey, *Refiner Natural Gasoline Mfr.*, **18**, 486 (1939); *Oil Gas J.*, **38**, No. 28, 50 (1939).



The alkali aluminum chlorides are active catalysts for alkylation only when (a) the alkane is introduced in excess of the alkene to lessen the competitive reaction of polymerization, (b) alkenes of small size are utilized to decrease the polymerization tendency, (c) moderate rates of hydrocarbon input are maintained to obtain an appreciable alkylation, (d) optimum temperatures are used for the particular catalyst selected, and (e) fresh catalyst is used. The alkali aluminum chlorides were selective toward alkylation of isobutane for about 5 hours and functioned thereafter as polymerization catalysts.

IV. DEHYDROGENATION OF ALIPHATIC HYDROCARBONS

Thermal dehydrogenation of alkanes to alkenes, alkadienes, and alkynes has been recognized for a long time, but the reaction shows no selective production of alkenes and alkadienes in high yields.¹⁴¹ In recent years, catalysts have been found which are selective and bring about almost quantitative dehydrogenation of ethane, propane, *n*-butane, and isobutane to the corresponding alkenes, and of butenes, isobutene, and pentenes to alkadienes. Cracking of the carbon-carbon linkages is eliminated for the most part in the catalytic reaction while thermal dehydrogenation is accompanied by considerable cracking. Commercial importance of the resulting alkenes is found in the manu-

¹⁴¹ Egloff, "Reactions of Pure Hydrocarbons," Reinhold Publishing Corp., New York (1937), pp. 34, 279

facture of high-octane-rating gasoline by conversion of the butenes into isoöctanes through alkylation and hydrogenation. The isobutene and butadiene from butanes are used as basic materials in the production of synthetic rubber and resins.

Dehydrogenation of Alkanes. A comparison of thermal with catalytic dehydrogenation, at 600° and 1 atmosphere pressure of *n*-butane, shows only 14 per cent conversion to butenes in the thermal reaction while over 95 per cent conversion was obtained in the catalytic reaction.¹⁴² Dehydrogenation is considered thermodynamically impossible except at elevated temperatures, and alkanes, especially the higher ones, decompose at these temperatures.¹⁴³ The equilibrium constants for the first four alkanes from 350° to 500° in reactions catalyzed by chromium oxide gel, with no appreciable side reactions, show that dehydrogenation increases with temperature and the shorter chains are more stable than the longer chains at higher temperatures as indicated in Table II.

TABLE II

| <i>K</i> | 350° | 400° | 450° | 500° |
|---|---------|---------|---------|--------|
| $\frac{(C_2H_4)(H_2)}{C_2H_6}$ | | 0.00015 | 0.00076 | 0.0032 |
| $\frac{(C_3H_6)(H_2)}{C_3H_8}$ | 0.00038 | 0.0022 | 0.0074 | |
| $\frac{(CH_3CH_2CH=CH_2)(H_2)}{CH_3CH_2CH_2CH_3}$ | 0.00045 | 0.0022 | 0.0075 | |
| $\frac{(trans-CH_3CH=CHCH_3)(H_2)}{CH_3CH_2CH_2CH_3}$ | 0.00083 | 0.0039 | 0.014 | |
| $\frac{(cis-CH_3CH=CHCH_3)(H_2)}{CH_3CH_2CH_2CH_3}$ | 0.00052 | 0.0025 | 0.0087 | |
| $\frac{((CH_3)_2C=CH_2)(H_2)}{(CH_3)_2CHCH_3}$ | 0.0017 | 0.010 | 0.042 | |

The first requisite of the catalyst is that it must promote splitting off of hydrogen without cleavage of the carbon-carbon bond.¹⁴⁴ Compounds which catalyze dehydrogenation at lower temperatures are not used unless capable of selective activity above 500°, since equilibrium shifts toward the alkane below 500°. Accumulation of carbonaceous deposits and other materials foreign to the reaction deactivates the catalyst; therefore the catalyst must be capable of rapid regeneration

¹⁴² Grosse, Ipatieff, Egloff, and Morrell, *Proc. Am. Petroleum Inst.*, **20** III, 110 (1939)

¹⁴³ Frey and Huppke, *Ind. Eng. Chem.*, **25**, 54 (1933).

¹⁴⁴ Grosse and Ipatieff, *ibid.*, **32**, 268 (1940).

under commercial conditions.^{144, 145} Excessive temperatures may disrupt the physical structure of the catalyst, and then regeneration is not possible.¹⁴⁵

From consideration of chemical composition, the oxides of the transition metals of groups IV, V, and VI, such as chromium, molybdenum, vanadium, titanium, and cerium, are the best catalysts.¹⁴⁴ Chromium oxide has been used most extensively. When used in reactions of hydrocarbons having six or more carbon atoms, it also catalyzes cyclization of the carbon chain. The oxide is more active when supported on a carrier of relatively lower activity such as alumina. Activated alumina alone promotes dehydrogenation but is less effective than chromium oxide on alumina.¹⁴⁵ Chromium oxide is active in the gel form at 400° but is unstable at 500°. The gel form is not useful for dehydrogenation since equilibrium is on the alkane side at lower temperatures. Alumina also modifies the activity of compounds which are too active for use as dehydrogenation catalysts. Iron oxide in gel form, for example, catalyzes disruption of the hydrocarbon molecule, but promotes selective dehydrogenation when employed on an alumina carrier. Aluminum oxide was used as carrier for nickel oxide, vanadyl sulfate, zinc oxide, and reduced nickel; it rendered them effective in reactions carried out at 500° to 600°. The high adsorptive activity as well as the porous solid structure of alumina seems to be the reason for its suitability. Relation of high adsorptive capacity to catalytic activity is evidenced by the necessity of small amounts of water or hydrogen sulfide in the reaction.

The temperature range suitable for catalytic dehydrogenation of alkanes¹⁴⁴ is between 500° and 750°. When chromium oxide on alumina is used, however, temperatures between 500° and 600° are adequate. The reaction is successfully carried out at atmospheric pressure. The readiness with which dehydrogenation takes place increases as the size of the hydrocarbon molecule increases up to a maximum at which cracking or carbon-carbon scission takes place.¹⁴³ As the time of reaction is lengthened, dehydrogenation increases to a maximum, after which secondary reactions begin to complicate the reaction. In experiments with copper on pumice, the following reactions, (2) and (3), predominated over (1), but the relative extent of reaction (1) was increased by shortening the contact time.¹⁴⁶



¹⁴⁵ Burgin, Groll, and Roberts, *Oil Gas J.*, **37**, No. 17, 48 (1940).

¹⁴⁶ Matignon, Kling, and Florentin, *Compt. rend.*, **194**, 1040 (1932).

The presence of small amounts of water vapor, about 0.1 mole per cent introduced with the hydrocarbon, seems to be necessary.¹⁴⁷ Without this moisture, the catalyst is inefficient, but with excess moisture, the activity is also decreased. The action of the water is probably the formation of a monomolecular layer over the catalyst and regulation of the state of hydration of the alumina. The postulation has been made that the monomolecular layer is the seat of dehydrogenation and that the reaction may occur between the carbon-hydrogen bonds of the alkane and the activated hydrogen-oxygen bonds in the adsorbed state. Hydrogen sulfide and other compounds containing hydrogen bonded to an electronegative element function in the same manner as water.

Dehydrogenation of Alkenes. Conjugated alkadienes result from the catalytic dehydrogenation of the alkenes. Whether 1- or 2-butene was used as starting material, the final product was 1,3-butadiene.¹⁴⁸ Likewise the pentenes and methylbutenes yielded 1,3-pentadiene and methyl-1,3-butadiene, respectively. A tendency to form allene type products was not observed with butenes and pentenes, and propene yielded predominately carbon and hydrogen when subjected to dehydrogenation conditions. Alkynes are not formed in the catalytic dehydrogenation of alkenes, and starting with butadienes under dehydrogenation conditions, the reaction yields liquid polymerization and condensation products. The catalysts used for dehydrogenation of alkanes to alkenes are effective in producing alkadienes from alkenes. The equilibrium



is shifted to the right by both increased temperature and diminished pressure. The amount of butadiene from 2-butene at 700° was also increased by the presence of magnesium oxide, zinc oxide, silica gel, platinum, iron, copper, and charcoal.¹⁴⁹ Yields decreased in these experiments when the velocity of the incoming butene was increased or the time of reaction shortened. Carbonaceous deposits are formed to a greater extent in the dehydrogenation of alkenes than of alkanes. By shortening the contact time, carbon formation may be minimized.¹⁴⁸

V. DEHYDROCYCLIZATION OF ALKANES AND ALKENES TO AROMATIC HYDROCARBONS

For a long time, aliphatics and alicyclics have been known to give low yields of aromatic hydrocarbons at high temperatures by cracking.¹⁴¹

¹⁴⁷ Beeck, *Nature*, **136**, 1028 (1935).

¹⁴⁸ Grosse, Morrell, and Mavity, *Ind. Eng. Chem.*, **32**, 309 (1940).

¹⁴⁹ Fedorov, Smirnova, and Semenov, *J. Applied Chem. (U.S.S.R.)*, **7**, 1166 (1934) [*C. A.*, **29**, 5808 (1935)].

In recent years, however, a new reaction of catalytic dehydrocyclization or aromatization has been used to convert alkanes and alkenes of six to ten carbon atoms into aromatic hydrocarbons in almost theoretical yields. The products obtained are those predicted when rearrangement of the hydrocarbon skeleton prior to cyclization does not take place. For example, *n*-hexane or *n*-hexene and *n*-heptane or *n*-heptene yield benzene and toluene respectively. Thermodynamic considerations indicate that dehydrocyclization should be carried out¹⁵⁰ above 300°. Since the aliphatic hydrocarbons decompose at these temperatures, aromatization requires the selection of a dehydrogenating catalyst that does not split the carbon-carbon linkages. A catalyst which can readily be reactivated is necessary since the catalyst is poisoned by accumulation of hydrogen, water vapor, oxygen, by-products, and carbonaceous materials.^{150, 151} The more efficient catalysts are found in the oxides from metals of groups IV, V, and VI of the periodic table. Certain variations of these oxides promote an almost quantitative reaction.¹⁵² Alkenes, however, are not wholly eliminated as products of the reaction even with these catalysts.

Moldavskii and co-workers obtained, with chromium oxide as catalyst at about 470°, appreciable amounts of aromatics from the dehydrocyclization of alkanes having six to ten carbon atoms.¹⁵³ Molybdenum sulfide and activated carbon also caused dehydrocyclization. Octane was converted into 1,2-dimethylbenzene by the catalytic action of zinc oxide, titanium oxide, molybdenum oxide, or molybdenum sulfide at temperatures of 400° to 550°. ¹⁵⁴ Activated wood charcoal or carbon deposited on iron turnings promoted the conversion of octane into 1,2-dimethylbenzene and of 2,5-dimethylhexane into 1,4-dimethylbenzene.¹⁵⁵ Other experimenters using platinized charcoal at about 310° obtained small yields of aromatics.¹⁵⁶ Platinum with nickel catalyzed the reaction at 260° to 350°. ¹⁵¹ Nickel with alumina promoted dehydro-

¹⁵⁰ Taylor and Turkevich, *Trans. Faraday Soc.*, **35**, 921 (1939).

¹⁵¹ Zelinsky, Kasanskii, Liberman, Lossik, Plate, and Serguienko, *Compt. rend. acad. sci. U.R.S.S.*, **27**, 443 (1940); Kazanskii, Plate, Bulanova, and Zelinsky, *ibid.*, **27**, 658 (1940); Kazanskii, Serguienko, and Zelinsky, *ibid.*, **27**, 664 (1940).

¹⁵² Grosse, Morrell, and Mattox, *Ind. Eng. Chem.*, **32**, 528 (1940).

¹⁵³ Moldavskii, Kamusher, and Kobyl'skaya, *J. Gen. Chem. (U.S.S.R.)*, **7**, 169 (1937); *Refiner Natural Gasoline Mfr.*, **18**, 118 (1939); Moldavskii and Kamusher, *Compt. rend. acad. sci. U.R.S.S.*, **10**, 355 (1936).

¹⁵⁴ Moldavskii, Kamusher, and Kobyl'skaya, *J. Gen. Chem. (U.S.S.R.)*, **7**, 1835 (1937) [*C. A.*, **32**, 508 (1938)].

¹⁵⁵ Moldavskii, Bezprozvannaya, Kamusher, and Kobyl'skaya, *ibid.*, **7**, 1840 (1937) [*C. A.*, **32**, 508 (1938)].

¹⁵⁶ Kazanskii, Plate, and Goledman, *Compt. rend. acad. sci. U.R.S.S.*, **23**, 250 (1939); Kazanskii and Plate, *J. Gen. Chem. (U.S.S.R.)*, **9**, 496 (1939) [*C. A.*, **33**, 9294 (1939)]; Kazanskii and Plate, *Ber.*, **69**, 1862 (1936).

cyclization of *n*-octane and *n*-decane, but this catalyst also caused the side chain to split, yielding toluene and alkanes as the final products.¹⁵⁷ Chromium with copper and phosphoric acid catalyzed dehydrocyclization of *n*-heptane, *n*-decane, and isodecane, but yields were less than 50 per cent.¹⁵⁸ Chromium borate was effective but its activity decreased rapidly.¹⁵⁹

The oxides of metals of groups IV, V, and VI give much better results than other catalysts which promote dehydrocyclization, and the form in which they are used is important. With chromium oxide gel at about 470°, 89 per cent toluene was obtained from heptane and 90 per cent aromatic products from heptene.¹⁵⁰ With freshly prepared chromic oxide, the aromatic yield was composed of almost 100 per cent benzene from *n*-hexane, 95 per cent toluene from *n*-heptane, and about 80 per cent 1,4-dimethylbenzene from 2,5-dimethylhexane.¹⁶⁰ The activity of previously ignited chromium oxide decreased much more rapidly than that of the non-ignited.¹⁵⁹ Chromium oxide deposited on the previously ignited compound, however, was more effective than either form alone.^{151, 159} On alumina, non-ignited chromium oxide is very good and may be readily regenerated with air. Vanadium, thorium, molybdenum, and uranium oxides were also more active when used on an alumina carrier. Chromium oxide is effective at lower temperatures than vanadium oxide.¹⁶¹ The comparative value of the oxides as catalysts was chromium, vanadium, and molybdenum > chromium and vanadium > chromium and molybdenum > chromium > vanadium and molybdenum.¹⁵² A mixture of cobalt oxide and chromium oxide on alumina also catalyzes aromatization, and this catalyst is readily regenerated.¹⁶²

The results of dehydrocyclization vary with the size and structure of the hydrocarbon used. The reaction is less successful if the compound must isomerize to a six-carbon chain before cyclization as in the case of the methylpentanes.¹⁶⁰ An increase in the size of the hydrocarbon molecule increases aromatization. *n*-Nonane produced about 38 per cent more aromatic products than did *n*-hexane. Cracking reactions, i.e., carbon-carbon cleavages, become more important with hydrocarbons having more than eight carbon atoms. In some hydrocarbons,

¹⁵⁷ Komarewsky and Riesz, *J. Am. Chem. Soc.*, **61**, 2524 (1939).

¹⁵⁸ Karzhev, Sever'Yanova, and Siova, *Oil Gas J.*, **37**, No. 4, 50 (1938); *Khim. Tverdogo Topliva*, **7**, 559 (1936).

¹⁵⁹ Kazanskii, Liberman, Plate, Serguienko, and Zelinsky, *Compt. rend. acad. sci. U.R.S.S.*, **27**, 446 (1940).

¹⁶⁰ Hoog, Verheus, and Zuiderweg, *Trans. Faraday Soc.*, **35**, 993 (1939).

¹⁶¹ Koch, *Brennstoff-Chem.*, **20**, 1 (1939).

¹⁶² Sergienko, *Bull. acad. sci. U.R.S.S.*, No. 1, 191 (1941).

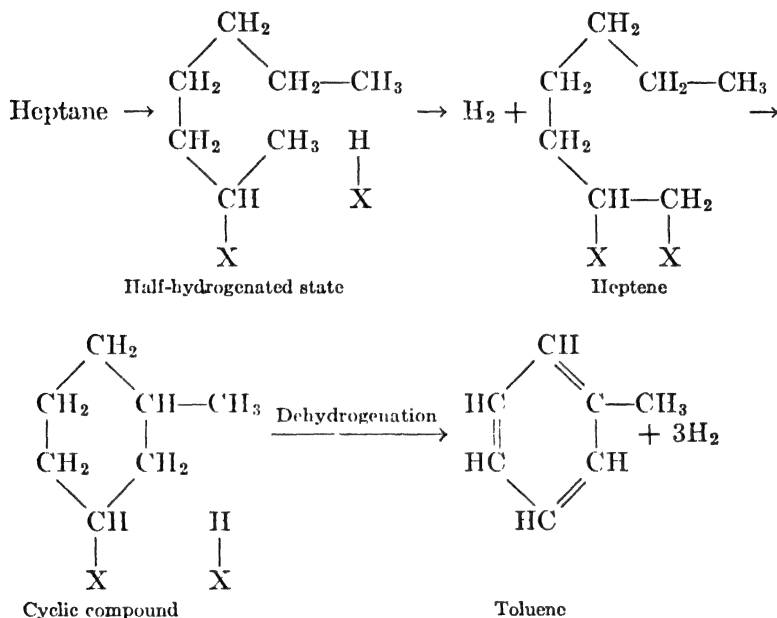
chain branching is observed to increase the yield of aromatics, but in others it seems to decrease aromatization. The difference between 2,5-dimethylhexane and 3-methylheptane indicates that branching favors aromatization, but the difference in the products of 3-methylheptane and *n*-octane shows the contrary. When compounds present alternative courses for ring closures, not all possibilities are realized. The aromatic yield from 3-methylheptane, for example, is about 35 per cent 1,2-dimethylbenzene, 5 per cent 1,3-dimethylbenzene, 55 per cent 1,4-dimethylbenzene, but only 5 per cent ethylbenzene. Two isomers are theoretically formed from both *n*-octane and *n*-nonane, but 80 per cent of the eight-carbon aromatic product is 1,2-dimethylbenzene and 90 per cent of the nine-carbon yield is 1-methyl-2-ethylbenzene. Ring closures seem to involve secondary carbon atoms preferentially, and compounds which have the shortest possible side chains result if their formation does not require isomerization of the carbon skeleton. During the aromatization of alkanes in the presence of chromium oxide 2- and 3-alkenes are also formed. The positions of the double bonds are probably determined by the catalyzed isomerization of 1-alkenes.

Aromatization of alkenes, as of alkanes, increases with the number of carbon atoms.¹⁶⁰ The position of the double bond may influence the reaction. Thirteen per cent more aromatics was obtained from 1-hexene than from 2-hexene but only 4 per cent more aromatics was obtained from 1-heptene than from 2-heptene. Dehydrocyclization of the alkenes occurs more readily than that of the alkanes.^{150, 160} The aromatization, however, is not correspondingly greater since the catalyst is more rapidly deactivated in alkene reactions by the greater occurrence of side reactions.¹⁶⁰ 1-Hexene yields 11.5 per cent more aromatics than *n*-hexane, and 2-octene yields 13 per cent more aromatics than *n*-octane.¹⁶⁰ A shifting of the double bond from the terminal position is found in the alkene products from chromium oxide-catalyzed reactions. The point of unsaturation of 1- and 2-heptene shifts to the 3-position.

Several possibilities may be offered for the course through which dehydrocyclization proceeds.¹⁶⁰ The alkane may form the aromatic in one step by a simultaneous cyclization and dehydrogenation. A second method is the primary formation of an alkene which may form either an aromatic directly, or an alicyclic which dehydrogenates to an aromatic, or an alkane may form an alicyclic which in turn yields an aromatic. Alkenes in the final reaction products may be accounted for by side reactions rather than by their formation as intermediates in the dehydrocyclization reaction, but data indicate that cyclization of alkanes occurs largely through dehydrogenation to the corresponding alkene. Although it is probable that the reaction proceeds partially through

formation of an alicyclic, very few and in some cases no alicyclic compounds have been found in the final products.^{159, 160, 163} Pitkethly and Steiner have proposed two mechanisms in which some of the intermediates exist in association with active centers on the catalytic surface.¹⁶³

Their data give evidence that alkenes are actually intermediate products but that cyclic compounds do not exist in an isolable form. The following mechanism, in which X represents an active center on the catalytic surface, has been proposed to coordinate the data of Rideal and the postulations of Pitkethly and Steiner:¹⁶⁴



The dehydrocyclization of alkanes, although discovered but a few years ago, is now in commercial operation. One plant costing over \$14,000,000 produces 30,000,000 gallons of toluene yearly, which is more than the total produced by all the coal carbonization units operating in the United States. The toluene will be converted into the explosive trinitrotoluene.

VI. PREPARATION OF THE HALOGEN DERIVATIVES OF ALIPHATIC HYDROCARBONS

The halogen derivatives of aliphatic hydrocarbons are prepared by action of the halogens and halogen-containing compounds. Alkyl bro-

¹⁶³ Pitkethly and Steiner, *Trans. Faraday Soc.*, **35**, 979 (1939).

¹⁶⁴ Twigg, *ibid.*, **35**, 1006 (1939); Rideal, *Proc. Cambridge Phil. Soc.*, **35**, 130 (1939).

midates and chlorides are produced with greater facility than iodides and fluorides since the iodination reaction is reversible and fluorination tends to be explosive. Bromination, while readily accomplished, has received less attention in the laboratory and is of less commercial importance than chlorination.

Chlorination or bromination of alkenes may be controlled so that substitution products are formed. As with the alkane substitutions, the mechanism of this reaction appears to be a radical chain mechanism.

The alkadienes and alkenynes usually form 1,4-addition compounds rather than simple addition products as observed with alkenes. The alkenynes also resemble the alkynes in some halogenation reactions.

The halogen substitution of alkynes requires the use of special reagents.

Halogenation of Alkanes

The reaction of alkanes with halogens is brought about by heat, light, and catalysts. There is considerable evidence that halogenation follows a chain-mechanism reaction, but the difficulty in isolating all intermediate compounds prevents establishment of one definite course of reaction. Activation energy calculations on the chlorination of methane as well as recent experimental data support a free-radical chain mechanism.

The facility with which halogenation takes place is largely determined by the halogen used. Fluorine derivatives of alkanes are usually prepared by indirect methods such as the reaction of bromo-, chloro-, or iodoalkanes with a metallic fluoride or the reaction between fluorine and charcoal. Chlorine has been studied almost exclusively in the halogenation reaction since it substitutes more readily than bromine.

Thermal Halogenation of Alkanes. Halogenation of alkanes takes place as a homogeneous reaction at elevated temperatures.^{165, 166, 167} The chlorination of lower alkanes is effected thermally¹⁶⁷ above 200° and has been studied at temperatures¹⁶⁸ over 1000°. Methane, ethane, propane, and butanes give appreciable yields of chlorinated products at about 300°.

The extent of polysubstitution depends on the rates of competing reactions.¹⁶⁵ Polysubstitution may be minimized by temperature control,^{169, 170} but a good yield of monochloride may be obtained at high

¹⁶⁵ Vaughan and Rust, *J. Org. Chem.*, **5**, 449 (1940).

¹⁶⁶ Pease and Walz, *J. Am. Chem. Soc.*, **53**, 382, 3728 (1931).

¹⁶⁷ Yuster and Reyerson, *J. Phys. Chem.*, **39**, 859 (1935).

¹⁶⁸ Mason and Wheeler, *J. Chem. Soc.*, 2282 (1931).

¹⁶⁹ Guyer and Rufer, *Helv. Chim. Acta*, **23**, 533 (1940).

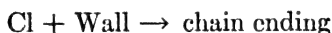
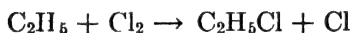
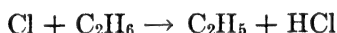
¹⁷⁰ Hass, McBee, and Weber, *Ind. Eng. Chem.*, **28**, 333 (1936).

temperatures, 800° to 900°, by rapid passage of the gases through the reaction tube.¹⁶⁸

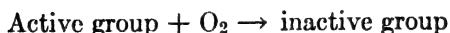
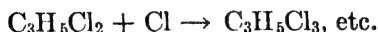
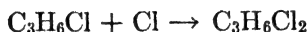
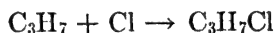
Both the mono- and dichlorination products give evidence that carbon skeleton rearrangements occur only as a result of pyrolysis.¹⁷¹ Liquid phase chlorination shows rates duplicated by vapor phase chlorination only at much higher temperatures.¹⁷⁰ In regard to the orientation of a second substituent, Hass and co-workers report that the presence of a halogen on a carbon hinders further substitution on that atom.¹⁷⁰

Uncatalyzed fluorine substitution proceeds under somewhat modified conditions. Moissan isolated carbon tetrafluoride from the fluorinated products of a low-temperature methane-fluorine reaction.¹⁷² Hexane was fluorinated at the temperature of an ice-salt bath by the introduction of the halogen diluted with nitrogen gas.¹⁷³ Fluorohexadecane was obtained when fluorine diluted with carbon dioxide was reacted with a carbon tetrachloride solution of *n*-hexadecane.¹⁷⁴

Experimental evidence indicates that thermal chlorination results, at least in part, from a chain mechanism. Observations have been made which support both a free-radical chain and a thermal chain initiated through bimolecular metatheses. The simple mechanism may be illustrated:¹⁶⁵



Yuster and Reyerson suggest chain-termination possibilities represented by the intermediates of the propane reaction:¹⁶⁷



¹⁷¹ Hass, McBee, and Weber, *ibid.*, **27**, 1190 (1935).

¹⁷² Moissan, *Compt. rend.*, **110**, 951 (1890).

¹⁷³ Fredenhagen and Cadenbach, *Ber.*, **67**, 928 (1934).

¹⁷⁴ Bockenmüller, *Ann.*, **506**, 20 (1933).

The production of chlorine atoms and the termination of chains on the wall of the reactor are indicated by dependence of the reaction on a surface. The fact that the presence or absence of moisture, carbon surfaces, and light does not affect the relative reaction rates of substitution indicates a chain reaction initiated at the wall.¹⁷⁰ The inhibitory effect of oxygen supports a free-radical chain mechanism.¹⁶⁵ An induction period also indicates the initiation of a chain reaction.

In consideration of experimental results^{170, 171, 175} on thermal chlorination of alkanes, the following generalizations may be offered:

1. A molar excess of alkane over halogen diminishes the amount of polychlorination.

2. Oxygen inhibits chlorination.

3. The presence of alkenes inhibits the chlorination of alkanes. The chlorination takes place, however, on the alkane.

4. Carbon skeleton rearrangements do not occur below temperatures at which pyrolysis takes place.

5. The relative rates of substitution are primary < secondary < tertiary, but the rates approach 1 : 1 : 1 at increasing temperatures.

6. The relative rates of primary, secondary, and tertiary substitution are not affected by moisture, carbon surfaces, or light.

7. Increased pressure causes increased relative rates of primary substitution.

8. The free-radical chain mechanism seems to offer a plausible explanation for thermal chlorination.

Catalytic Halogenation of Alkanes. Several types of substances accelerate the halogenation of alkanes. Effective materials are compounds which readily decompose to free radicals; metals and metallic salts, alone or dispersed on silica gel or pumice; activated carbon; and simultaneously reacting olefins. Ethane and chlorine react in the presence of tetraethyllead at 132°, a temperature about 150° lower than that required for purely thermal chlorination.¹⁶⁵ The catalytic action of this type of compound supports a chain mechanism.

Some metals and metallic salts accelerate halogenation reactions. The control of direct fluorination has been effected by modifying the reaction rate with a copper gauze catalyst.¹⁷⁶ Cupric chloride, cerous chloride, and ferric chloride are frequently used in the chlorination of alkanes.^{177, 178, 179} Bromination occurs with ferric bromide on pumice.

¹⁷⁵ Hass, McBee, and Hatch, *Ind. Eng. Chem.*, **29**, 1335 (1937).

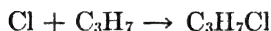
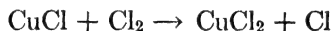
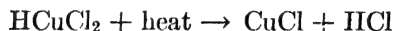
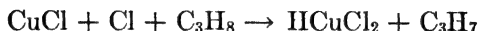
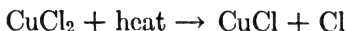
¹⁷⁶ Hadley, Young, Fukuhara, and Bigelow, paper presented at Am. Chem. Soc. Meeting, Cincinnati, 1940; Calfee, Fukuhara, and Bigelow, *J. Am. Chem. Soc.*, **61**, 3552 (1939); Calfee and Bigelow, *ibid.*, **59**, 2072 (1937).

¹⁷⁷ Giordani, *Ann. chim. applicata*, **25**, 163 (1935) [*C. A.*, **29**, 6206 (1935)].

¹⁷⁸ Zapan, *Thèses Faculté Sci. Univ. Paris*, 9 (1930) [*C. A.*, **26**, 77 (1932)].

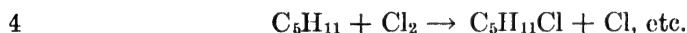
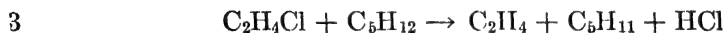
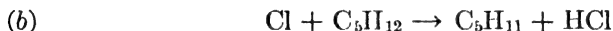
¹⁷⁹ Tomasik, *Przemysl Chem.*, **18**, 598 (1934) [*C. A.*, **29**, 6206 (1935)].

Activated cupric chloride on silica gel has been found to be more efficient than activated copper or aluminum oxide in the chlorination of propane at 324°; there is a heterogeneous reaction under these conditions, showing the following mechanism at the surface:¹⁸⁰



Antimony pentachloride catalyzes the chlorination of methane and ethane more effectively than titanous chloride, which in turn is more effective than stannous chloride.¹⁷⁸

Chlorination may also be catalyzed by simultaneously reacting olefins. Pentane in a mixture with ethene and chlorine undergoes substitution, and chloropentane is formed in preference to dichloroethane.¹⁸¹ Stewart and Weidenbaum¹⁸¹ have proposed a chain mechanism favoring propagation by the olefin intermediate rather than the pentane intermediate:



Reaction (a) is not as slow as (b), and consequently (a) is the favored course of reaction.

Alkanes may be chlorinated with sulfonyl chloride if a peroxide is present as catalyst.¹⁸² The reaction proceeds in the dark and is more rapid than photochlorination with chlorine gas. Introduction of a second substituent using benzoyl and lauroyl peroxide is comparatively difficult and takes place on the carbon atom farthest removed from the halogenated carbon, while substitution of a third chlorine is impossible with this reagent. Bromine is not displaced by chlorine from sulfonyl chloride.

Photohalogenation of Alkanes. Alkanes may be halogenated at low temperatures in the presence of either sunlight or artificial light. Photo-

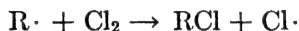
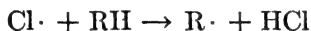
¹⁸⁰ Reyeerson and Yuster, *J. Phys. Chem.*, **39**, 1111 (1935).

¹⁸¹ Stewart and Weidenbaum, *J. Am. Chem. Soc.*, **57**, 2036 (1935).

¹⁸² Kharasch and Brown, *ibid.*, **61**, 2142 (1939).

chlorination is a process of progressive substitution and often becomes explosive.¹⁸³ Polyhalogenation can be partially eliminated through the use of less active forms of light. The ultra-violet ray does not seem to be the effective ray in chlorination.¹⁸⁴ Oxygen inhibits the chlorination process.^{185, 186}

The chain mechanism of reaction is very well established for photo-halogenation. The course of reaction begins with the dissociation of the diatomic halogen molecule to form "odd molecules" as a result of the absorption of one quantum of light by the original molecule. This "odd molecule" then starts the reaction which is carried on by the alternate formation and disappearance of this molecule. The chain is terminated by recombination of atoms, reaction of radicals, or a triple collision in which a third body, such as the wall, removes the energy.¹⁸⁷ Recent investigations support a chain mechanism which involves the "transitory existence of a free radical":¹⁸⁸



The quantum yield decreased with length of exposure indicating an increasing prevalence of chain termination reactions.¹⁸⁴ The quantum yields for the photochlorination of methane were of the order 10^4 molecules/ $h\nu$ in both ultra-violet light and light of wavelength 4358 Å.

Preparation of the Halogen Derivatives of Alkenes

With the exception of chlorine substitution on isobutene¹⁸⁹ and trimethylethene,¹⁹⁰ additions have been considered the only reactions between alkenes and halogens until recently when it was found that substitution is a type of reaction exhibited by alkenes.

The unsaturated carbons of alkenes add halogen atoms from the molecular halogens, hydrogen halides, and other compounds containing a reactive halogen atom. Substitution complicates the addition reaction of halogens at elevated temperatures. Addition of hydrogen halides normally follows Markovnikov's rule (p. 638) that the halogen atom

¹⁸³ Egloff, Schaad, and Lowry, *Chem. Rev.*, **8**, 1 (1931).

¹⁸⁴ Coehn and Cordes, *Z. physik. Chem.*, **B9**, 1 (1930).

¹⁸⁵ Deanesley, *J. Am. Chem. Soc.*, **56**, 2501 (1934).

¹⁸⁶ Jones and Bates, *ibid.*, **56**, 2282 (1934).

¹⁸⁷ Rollefson, *J. Phys. Chem.*, **42**, 773 (1938).

¹⁸⁸ Brown, Kharasch, and Chao, *J. Am. Chem. Soc.*, **62**, 3435 (1940).

¹⁸⁹ Sheshukov, *J. Russ. Phys. Chem. Soc.*, **16**, 478 (1884).

¹⁹⁰ Kondakov, *ibid.*, **17**, 290 (1885).

goes to the unsaturated carbon atom bearing the least hydrogens. There are exceptions, however, and attempts have been made to explain abnormal orientations resulting from peroxides and solvents.

Halogen Substitution of Alkenes. The substitution of halogen into alkenes compares with the halogenation of alkanes. Thermal and "induced" substitutions are common to both. Similar mechanisms explain their respective courses of reaction. It is questionable, however, whether any of these are induced substitutions or substitutions depending on the specific character of the alkene. Stewart and Weidenbaum found the pentene reaction comparable with the chlorine substitution of pentane as induced by an ethene-chlorine mixture.¹⁹¹

Substitution of alkenes at high temperatures is in many respects comparable to thermal substitution of alkanes. The presence of the alkene also has been shown to hinder the total chlorine substitution of the mixture.¹⁹² The presence of other alkenes, especially propene, also inhibits substitution in ethene, while some substitution preferentially occurs on the saturated carbons of the alkene inhibitor. The substitution reaction takes place exclusively above a critical temperature range while below this range the reaction is addition. The temperature range varies with each hydrocarbon.¹⁹³

| ALKENE | CRITICAL TEMPERATURE RANGE, °C. |
|-----------|---------------------------------|
| 2-Pentene | 125-200 |
| 2-Butene | 150-225 |
| Propene | 200-350 |
| Ethene | 250-350 |

Bromine substitution at high temperatures is greater than that of chlorine; but near the lower limit of the critical range, bromine substitution scarcely occurs. This may be explained by the relatively greater dissociation of bromine at the elevated temperature. The temperature ranges of the various hydrocarbons indicate that ease of substitution is least in hydrocarbons having two primary carbon atoms on the double bond; increases when the hydrocarbon has one secondary atom on the double linkage; is even greater with two secondary atoms on the double bond; and substitution is predominant when the hydrocarbon has an unsaturated tertiary atom. It appears that substitution proceeds more readily to yield allyl-type products than the vinyl type. The production of allyl-type products falls in line with the proved greater ease of alkane substitution over alkene substitution.

¹⁹¹ Stewart and Weidenbaum, *J. Am. Chem. Soc.*, **58**, 98 (1936).

¹⁹² Rust and Vaughan, *J. Org. Chem.*, **5**, 472 (1940).

¹⁹³ Groll and Hearne, *Ind. Eng. Chem.*, **31**, 1530 (1939).

Both substitution and addition of chlorine by alkenes at high temperatures seem to occur largely by radical chain mechanisms, but reactions at surfaces and gas-phase bimolecular associations and metatheses probably also enter into the total reaction.¹⁹² Surface effects give some evidence of both bimolecular association and chain initiation. Calculations based on activation energies slightly favor chain mechanisms over bimolecular processes.¹⁹⁴

Addition of Halogen to Alkenes. Addition of chlorine to alkenes takes place with comparative ease. Reactivity seems to increase with the size of the alkene molecule.¹⁹⁵ A study has been made on pure ethene and chlorine gases reacting at 20° in the absence of light. The reaction was complicated by substitution which produced trichloroethane.^{196, 197} Oxygen slowed down the total reaction rate and tended to eliminate substitution.¹⁹⁶ An induction period was observed which terminated by the formation of a liquid film on the wall of the reactor, and the reaction proceeded rapidly from this point. These observations indicate an autocatalytic reaction involving chain mechanism. Stewart and Smith postulate an activated liquid complex of dichloroethane as the intermediate which catalyzes addition.¹⁹⁸

Normal addition has been observed on tertiary carbon atoms at the double bond, but the substitution reaction predominates.^{199, 200, 201} The solvent used is an important factor in alkene reactions.

With bromine, alkenes undergo a reaction similar to that observed with chlorine. The uncatalyzed addition of bromine to ethene at 16° in the absence of light is a surface reaction, and simple addition results unless bromine is present in excess so that supplementary reactions are induced. Moisture accelerates this reaction probably by surface action rather than by effect on the reacting substances in the bulk phase.²⁰²

Iodine forms less stable compounds with alkenes than do the other halogens. In the gaseous phase, diiodoethane undergoes homogeneous decomposition which may be accelerated by iodide ions.^{203, 204} The reaction of ethene gas with iodine was reported probably to take place

¹⁹⁴ Sherman, Quimby, and Sutherland, *J. Chem. Phys.*, **4**, 732 (1936).

¹⁹⁵ Mamedaliev, *Azerbaïdzhanskoe Neftyanoe Khoz.*, No. 3, 67 (1935) [*C. A.*, **29** 6205 (1935)].

¹⁹⁶ Stewart and Smith, *J. Am. Chem. Soc.*, **51**, 3082 (1929).

¹⁹⁷ Bahr and Zieler, *Z. angew. Chem.*, **43**, 233 (1930).

¹⁹⁸ Stewart and Smith, *J. Am. Chem. Soc.*, **52**, 2869 (1930).

¹⁹⁹ Burgin, Engs, Groll, and Hearne, *Ind. Eng. Chem.*, **31**, 1413 (1939).

²⁰⁰ D'yakonov and Tischenko, *J. Gen. Chem. (U.S.S.R.)*, **9**, 1258 (1939) [*C. A.*, **34** 710 (1940)].

²⁰¹ Tischenko, *J. Gen. Chem. (U.S.S.R.)*, **8**, 1232 (1938) [*C. A.*, **33**, 4190 (1939)].

²⁰² Williams, *J. Chem. Soc.*, 1758 (1932).

²⁰³ Sherman and Sun, *J. Am. Chem. Soc.*, **56**, 1096 (1934).

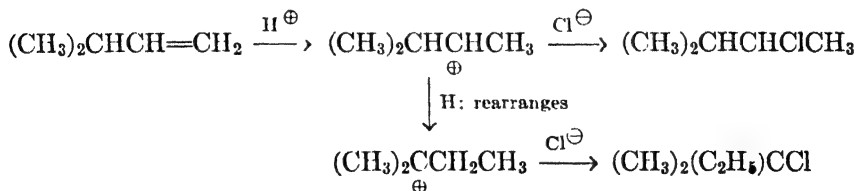
²⁰⁴ Mooney and Reid, *J. Chem. Soc.*, 2597 (1931).

on the surface of solid iodine.²⁰⁴ The velocity of this addition was much greater than that of the homogeneous reaction in carbon tetrachloride. With iodine, as was observed in the case of bromine, velocity of addition is enhanced by the presence of methyl groups on the unsaturated carbon atoms.²⁰⁵

Addition of Hydrogen Halides to Alkenes. The alkenes add halogen acids in the order: $\text{HI} > \text{HBr} > \text{HCl} > \text{HF}$. Addition takes place more readily with propene than with ethene and even more readily with butenes and higher homologs. With some exceptions which have been attributed to intramolecular rearrangements, properties peculiar to a specific compound, and effects of peroxides, solvents, and catalysts, orientation follows the Markovnikov rule.

Addition of hydrogen fluoride to alkenes has been accomplished, although activation energy calculations show that less energy is required for the cleavage of the carbon-carbon bond than for the addition of hydrogen fluoride to ethene.²⁰⁶ Grosse and Linn prepared ethyl, isopropyl, *tert.*-butyl, and *tert.*-pentyl fluorides by uncatalyzed addition of hydrogen fluoride to the alkene.²⁰⁷

Ethyl chloride may be formed by addition of hydrogen chloride to ethene at temperatures sufficiently low to avoid reversibility of equilibrium. It was believed that propene and hydrogen chloride did not react in the gaseous phase at relatively high temperatures, but with increased pressure the reaction took place.²⁰⁸ The reaction rate increased with temperature as long as the density decrease was not relatively greater than the temperature increase.²⁰⁹ Likewise, the rate of the liquid reaction increases with temperature until the density begins to decrease rapidly. These results have been interpreted as showing that the "structure" common to the liquid state favors high reaction rates. In hydrogen chloride addition to 3-methyl-1-butene both the secondary and tertiary products are obtained.²¹⁰ The formation of the tertiary product was attributed to a rearrangement of an intermediate:



²⁰⁵ Bythell and Robertson, *ibid.*, 179 (1938).

²⁰⁶ Sun and Sze, *J. Chinese Chem. Soc.*, **5**, 1 (1937).

²⁰⁷ Grosse and Linn, *J. Org. Chem.*, **3**, 27 (1938).

²⁰⁸ Sutherland and Maass, *Can. J. Research*, **5**, 48 (1931).

²⁰⁹ Holder and Maass, *ibid.*, **16B**, 453 (1938).

²¹⁰ Whitmore and Johnston, *J. Am. Chem. Soc.*, **55**, 5020 (1933).

Addition of hydrogen bromide compares with that of hydrogen chloride. Compounds with equally hydrogenated unsaturated carbon atoms cannot be classified under Markovnikov's rule, and published data do not warrant set rules of orientation.

The more reactive hydrogen iodide forms addition compounds with alkenes, but the reversibility of the reaction limits success in obtaining good yields.²¹¹ With the higher alkenes Tuot obtained polyiodides instead of monoiodides because hydrogen iodide dissociates more rapidly than it "fixes" to the hydrocarbon.²¹²

Orientation is at least partially influenced by the solvent used. In experiments on the addition of hydrogen bromide or iodide to propene and 1-pentene, primary halides were favored by solvents in the order of the relative values of internal pressure of the solvents.²¹³ The order of positive effect is propane > nitrobenzene > acetic acid > water. This order of effect is not in agreement with the order of the dielectric constants of the substances or with the order of their respective electronegativities. The presence of the highly ionized trichloroacetic acid increases the proportion of tertiary compound over that found in the reaction without solvent or with the comparatively weak acetic acid.²¹⁴

Catalytic Addition of Halogens and Hydrogen Halides to Alkenes.

Addition of halogens and halogen acids to alkenes is catalyzed by metals, metallic salts, and certain organic compounds. Most of these catalysts accelerate the normal addition defined by Markovnikov's rule. Abnormal addition, however, is catalyzed by a few metals.

The chlorination of ethene occurred in an iron reactor but not in a lead reactor under the same conditions.²¹⁵ Tetraethyllead accelerates addition, but its effectiveness on addition disappears at elevated temperatures where substitution sets in.¹⁹² Calcium halides promote addition and minimize substitution of alkenes.^{193, 216} Quinoline and hydrogen bromide also catalyze addition.²¹⁷

Since alkyl chlorides undergo thermal decomposition to olefins and hydrogen chloride, the use of a catalyst which will facilitate preparation below the decomposition temperature is desirable. Compounds containing a tertiary unsaturated carbon atom react at -80° without a

²¹¹ Pollissar, *J. Am. Chem. Soc.*, **52**, 956 (1930).

²¹² Tuot, *Compt. rend.*, **200**, 1418 (1935).

²¹³ Ingold and Ramsden, *J. Chem. Soc.*, 2746 (1931).

²¹⁴ Michael and Weiner, *J. Org. Chem.*, **5**, 389 (1940).

²¹⁵ Dobryanskii, Gutner, and Shchigel'skaya, *Trans. State Inst. Applied Chem (U.S.S.R.)*, **24**, 5 (1935) [*C. A.*, **29**, 7271 (1935)].

²¹⁶ Conn, Kistiakowsky, and Smith, *J. Am. Chem. Soc.*, **60**, 2764 (1938).

²¹⁷ Antikrishnan and Ingold, *J. Chem. Soc.*, 984 (1935).

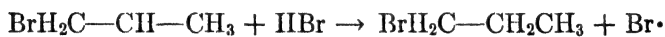
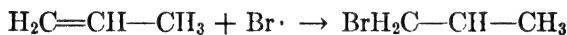
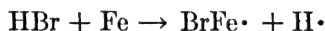
catalyst.^{218, 219, 220} Aluminum chloride brought about reaction between alkenes containing —C=C— groupings and dry hydrogen chloride at



—78° . Ferric,^{221, 222} stannous,²²³ stannic, mercuric,²²¹ nickel, aluminum, and calcium chlorides on silica gel acted as satisfactory catalysts. Addition of hydrogen chloride and bromide to ethene is accelerated by the corresponding anhydrous bismuth halide.²²⁴

Certain metals catalyze "abnormal addition," the bromine atom from hydrogen bromide adding to the more highly hydrogenated unsaturated carbon.^{225, 226, 227}

In order to catalyze abnormal addition, it appears that on reaction with anhydrous hydrogen bromide the metal must form a metal bromide which is neither a strong accelerator of normal addition nor a powerful inhibitor of abnormal addition.²²⁶ The mechanism seems to be similar to that of the peroxide-catalyzed abnormal addition and involves the following steps:



In the presence of peroxides, a liquid phase reaction mixture of hydrogen bromide and 1-alkene produces considerable quantities of 1-bromoalkane while the same mixture without peroxides yields a predominance of 2-bromoalkane. The latter isomer is predicted by Markovnikov's rule and is designated as the "normal" product. Some solvents seem to direct the bromine atom to the abnormal position in the absence of peroxides, but others inhibit abnormal orientation even in the presence of peroxides. Peroxides accelerate the rate of normal addition of hydrogen iodide,²²⁸ but have no effect on the speed of addition of hydro-

²¹⁸ Leendertse, *Rec. trav. chim.*, **57**, 795 (1938).

²¹⁹ Leendertse, Tulleners, and Waterman, *ibid.*, **52**, 515 (1933).

²²⁰ Leendertse, Tulleners, and Waterman, *ibid.*, **53**, 715 (1934).

²²¹ Brouwer and Wibaut, *ibid.*, **53**, 1001 (1934).

²²² Kharasch, Kleiger, and Mayo, *J. Org. Chem.*, **4**, 428 (1939).

²²³ Petrov and Milovanova, *Acta Univ. Voronegiensis*, **9**, No. 3, 145 (1937) [*C. A.*, **32**, 7014 (1938)].

²²⁴ Wibaut, *Z. Elektrochem.*, **35**, 602 (1929) [*C. A.*, **24**, 1076 (1930)].

²²⁵ Urushibara and Takebayashi, *Bull. Chem. Soc. Japan*, **11**, 692 (1936).

²²⁶ Kharasch, Haefele, and Mayo, *J. Am. Chem. Soc.*, **62**, 2047 (1940).

²²⁷ Urushibara and Simamura, *Bull. Chem. Soc. Japan*, **14**, 323 (1939).

²²⁸ Kharasch and Hannum, *J. Am. Chem. Soc.*, **56**, 1782 (1934).

gen chloride.^{222, 229} Hydrogen iodide inhibits abnormal addition even in the reaction of hydrogen bromide in the presence of peroxides.²³⁰ Hydrogen fluoride and hydrogen chloride undergo endothermic reactions which will not support the rapid, long-chain reactions necessary for abnormal addition.²³¹ Although the role of the peroxide has not been definitely established, it seems almost certain that abnormal addition proceeds by a rapid chain reaction.

The amount of peroxide catalyst is related to the composition of products. The yield of abnormal product from 2-isopentene increased from about 77 to 92 per cent with an increase of ascaridole from 0.002 molar to 0.02 molar.²³² Solvents influence the reaction considerably. In the absence of peroxides, abnormal hydrogen bromide addition to 1-pentene and 1-heptene proceeded in the presence of glacial acetic acid, heptane, or carbon tetrachloride, but aqueous hydrogen bromide gave the normal product.²³³ Kharasch, however, disputed this work since he obtained the normal product of 1-pentene in the presence of glacial acetic acid or propionic acid under antioxidant conditions.²³⁴ The solvents affected the velocity of the addition but had no directive influence. Appreciable quantities of the abnormal products were obtained in the presence of peroxides with ether at -78° , with acetic acid at 0° , and with small amounts of methanol or ethanol at 0° .²³²

The results of peroxide-catalyzed as well as metal-catalyzed abnormal addition reactions support chain reactions.^{226, 227} Formation of abnormal isomers through rearrangement does not explain the effect since addition of peroxides to normal isomers does not bring about rearrangement.²³⁵ Michael and Weiner offer an interpretation of solvent action involving reversed relative electronegativity of the carbon atoms.²³² Smith postulates a chain mechanism but disagrees with Kharasch on the hypothesis that bromine atoms propagate the reaction.²³⁶ According to Kharasch, normal addition occurs through a chain mechanism involving polar ions and molecules while abnormal addition proceeds through a bromine atom chain mechanism. The proposed role of the peroxide and of chain propagation in abnormal addition is shown in the following example:²³⁷

²²⁹ Smith, *Chemistry & Industry*, 833 (1937).

²³⁰ Kharasch, Norton, and Mayo, *J. Am. Chem. Soc.*, **62**, 81 (1940).

²³¹ Mayo and Walling, *Chem. Rev.*, **27**, 351 (1940).

²³² Michael and Weiner, *J. Org. Chem.*, **4**, 531 (1939).

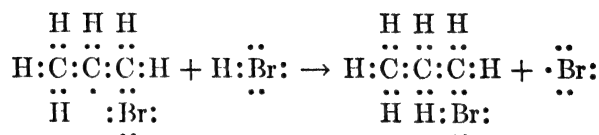
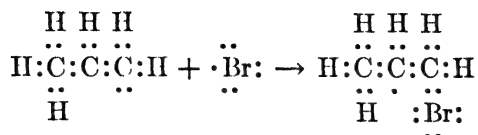
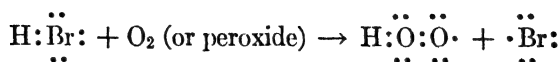
²³³ Sherrill, Mayer, and Walther, *J. Am. Chem. Soc.*, **56**, 926 (1934).

²³⁴ Kharasch, Hinckley, and Gladstone, *ibid.*, **56**, 1642 (1934).

²³⁵ Kharasch and Hinckley, *ibid.*, **56**, 1212 (1934).

²³⁶ Smith, *Chemistry & Industry*, 461 (1938)

²³⁷ Kharasch, Engellmann, and Mayo, *J. Org. Chem.*, **2**, 288 (1937).



The inhibitory effect of antioxidants is probably caused by their efficiency as chain breakers.²²⁶

Photohalogenation of Alkenes. Light accelerates addition of halogens and halogen acids to alkenes. It seems to have no orienting influence on hydrogen halide addition to the double bond and catalyzes both normal and abnormal reactions.²³⁸ Photohalogenation is important since it makes possible a study of chain mechanisms of halogenation.

The reaction rate seems to be proportional to light intensity and also to the concentrations of both reactants.²³⁹ The velocity of photoiodination of 2-pentene is proportional to the square root of the intensity of radiation absorbed.²⁴⁰

Experimental evidence indicates that photoaddition reactions are of considerable chain length.²⁴¹ Chain initiation is probably brought about through the production of a halogen atom by a quantum of light with propagation through a halogen atom or free radical. The chain-breaking reaction differs with single cases. Kinetic studies offered no basis for chain propagation through triatomic halogens as postulated by Rollefson.²⁴²

Preparation of Halogen Derivatives of Alkadienes

Halogens and alkadienes form dihaloalkenes which may be isolated under certain conditions and which undergo further halogenation to produce tetrahaloalkanes. The halogen acids yield corresponding haloalkenes and dihaloalkanes. 1,4-Addition products often occur with conjugated unsaturated systems.

The reaction of gaseous butadiene and bromine is essentially a sur-

²³⁸ Kharasch and Mayo, *J. Am. Chem. Soc.*, **55**, 2468 (1933).

²³⁹ Forbes and Nelson, *ibid.*, **59**, 693 (1937).

²⁴⁰ Ghosh and Bhattacharyya, *Science and Culture*, **3**, 120 (1937) [*C. A.*, **32**, 414 (1938)]

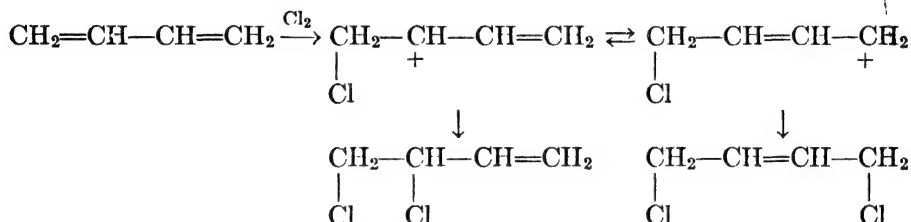
²⁴¹ Schumacher, *Angew. Chem.*, **49**, 613 (1936).

²⁴² Booher and Rollefson, *J. Am. Chem. Soc.*, **56**, 2288 (1934).

face reaction.^{243, 244, 245} Since coating of the surface with paraffin has little effect on the reaction, it occurs at the surface of the reaction film rather than of the container.²⁴⁵ This phenomenon is further evidenced by the fact that the rate increases until the walls are covered by a unimolecular layer of reactants and then becomes constant. Experimental data indicate a chain reaction initiated at a wall and broken by oxygen.²⁴³

Reaction of 2-methyl-1,3-butadiene with chlorine in carbon tetrachloride yielded the 1,4-compound predominantly as addition product and an appreciable quantity of 1-chloro-2-methyl-1,3-butadiene which indicates a substitution reaction.²⁴⁶

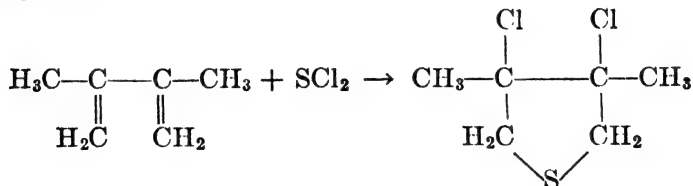
The reaction of butadiene with chlorine in carbon disulfide yielded twice as much 1,2-addition product as 1,4-product.²⁴⁷ The following course was postulated for formation of the two dichloro compounds:²⁴⁸



A suggestion that rearrangement to the 1,4-compound follows formation of the 1,2-isomer falls in line with the relative difficulty in breaking the carbon-bromine linkage and the fact that greater proportions of 1,4-compound are found in the bromine than in the chlorine reaction.

3-Bromo-1-butene was reported as the product from a reaction carried out under extreme antioxidant conditions.²⁴⁹ This product is evidence of an initial 1,2-addition. Peroxide addition to a mixture of isomers favored rearrangement of the 1,2-isomer to the 1,4-compound.

Sulfur chloride and 2,3-dimethylbutadiene in the presence of stannic chloride form a cyclic compound, 3,4-dichloro-3,4-dimethyl-2,5-dihydrothiophene.²⁵⁰



²⁴³ Heisig, *ibid.*, **58**, 1095 (1936).

²⁴⁴ Heisig and Davis, *ibid.*, **55**, 1297 (1933).

²⁴⁵ Heisig and Wilson, *ibid.*, **57**, 859 (1935).

²⁴⁶ Jones and Williams, *J. Chem. Soc.*, 829 (1934).

²⁴⁷ Farmer, Lawrence, and Scott, *ibid.*, 510 (1930).

²⁴⁸ Muskat and Northrup, *J. Am. Chem. Soc.*, **52**, 4043 (1930).

²⁴⁹ Kharasch, Margolis, and Mayo, *J. Org. Chem.*, **1**, 393 (1936).

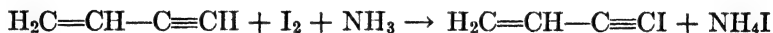
²⁵⁰ Backer and Strating, *Rec. trav. chim.*, **54**, 52 (1935).

With butadiene, however, tetrachlorobutane was the product rather than a cyclic sulfur compound.

Preparation of the Halogen Derivatives of Alkenynes

Compounds containing both double and triple carbon-carbon bonds undergo substitution by, and addition of, halogen atoms.

The triply bonded carbon substitutes a bromine or chlorine atom for hydrogen on reaction with the corresponding alkaline hypohalite solution and an iodine atom from a solution of iodine in potassium iodide.^{251, 252} Relative yields obtained were bromo > iodo > chloro. In ammonia which removes the hydrogen iodide produced, reaction with iodine yields a substitution product as follows:^{253, 254, 255, 256}



1,4-Addition seems to occur with conjugated alkenynes. The first step in hydrogen chloride addition to but-1-en-3-yne is 1,4-addition. Although the final product is 2-chloro-1,3-butadiene, the 4-chloro-1,2-butadiene intermediate was isolated.²⁵⁷ With excess hydrogen chloride, 2,4-dichloro-2-butene also forms. Cupric chloride, calcium chloride, and other salts seemed to increase greatly the rate of isomerization to the 2-chloro-1,3-butadiene. From aqueous hydrogen bromide reactions, only 2-bromo-1,3-butadiene and 2,4-dibromo-2-butene were isolated.²⁵⁸ This reaction was much faster than the hydrogen chloride reaction, however, and it is highly probable that the true course was a 1,4-addition followed by rearrangement.

Preparation of the Halogen Derivatives of Alkynes

Alkynes react with halogen by both substitution and addition. The substitution reactions occur under limited conditions and produce explosive compounds. Halogens, hydrogen halides, and acetyl halides are added to the triple bond. Haloalkenes from hydrogen halides and dihaloalkenes from halogens are isolated as the primary addition products in some reactions while further halogenation occurs in others with formation of only dihaloalkanes and tetrahaloalkanes. Halogen addi-

²⁵¹ Jacobsen and Carothers, *J. Am. Chem. Soc.*, **55**, 4667 (1933).

²⁵² Klebanskii, Volkenshtein, and Orlova, *J. Gen. Chem. (U.S.S.R.)*, **5**, 1255 (1935) [*C. A.*, **30**, 1025 (1936)].

²⁵³ Vaughn and Nieuwland, *J. Am. Chem. Soc.*, **54**, 787 (1932).

²⁵⁴ Vaughn and Nieuwland, *ibid.*, **55**, 2150 (1933).

²⁵⁵ Vaughn and Nieuwland, *J. Chem. Soc.*, 741 (1933).

²⁵⁶ Vaughn and Nieuwland, *J. Am. Chem. Soc.*, **56**, 1207 (1934).

²⁵⁷ Carothers, Berchet, and Collins, *ibid.*, **54**, 4066 (1932); Carothers and Berchet, *ibid.*, **55**, 2807 (1933).

²⁵⁸ Carothers, Collins, and Kirby, *ibid.*, **55**, 786 (1933).

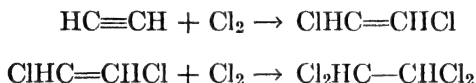
tion may be catalyzed by light, peroxides, metals, or metallic salts. The presence of peroxides has an effect similar to that observed with alkenes. Photohalogenations give evidence of chain reactions following courses similar to those postulated for alkanes and alkenes.

Alkynes substitute halogen atoms upon reaction with alkaline hypohalites. Iodine substitution may also be accomplished by use of iodine in liquid ammonia. An alkaline solution is necessary for substitution since addition occurs in acid solution with ultimate formation of a compound, $\text{RC}-\text{CHX}_2$.²⁵⁹ The substitution reaction is carried out in an



ice bath in the absence of light and air.²⁶⁰

Addition of halogens to alkynes in the presence of light is similar to the photohalogenation of alkenes. In the alkyne reaction, the simple addition product, a dihaloalkene, may be isolated, but tetrahaloalkanes form readily. Photochlorinations and photobrominations have been used to facilitate the study of chain mechanisms of reaction. A two-step reaction was postulated for the photochlorination of ethyne:²⁶¹



An induction period and inhibition by oxygen were observed, and these effects indicate a chain reaction. High quantum yields denote a chain reaction of considerable length in photobromination. Müller and Schumacher found a yield of 4×10^4 molecules/ $h\nu$ from reaction at 90° , 200 mm. total pressure.²⁶² The reaction theories involve bromine atoms, free radicals, and chain breaking by the disappearance of bromine at the wall. The proposed courses are:

- | | |
|---|---|
| I. (1) $\text{Br}_2 + h\nu = 2\text{Br}^{242}$ | II. (1) $\text{Br}_2 + h\nu = \text{Br} + \text{Br}^{263}$ |
| (2) $\text{Br} + \text{Br}_2 = \text{Br}_3$ | (2) $\text{Br} + \text{C}_2\text{H}_2 = \text{C}_2\text{H}_2\text{Br}$ |
| (3) $\text{Br}_3 + \text{C}_2\text{H}_2 = \text{C}_2\text{H}_2\text{Br}_3$ | (3) $\text{C}_2\text{H}_2\text{Br} = \text{C}_2\text{H}_2 + \text{Br}$ |
| (4) $\text{C}_2\text{H}_2\text{Br}_3 = \text{C}_2\text{H}_2\text{Br} + \text{Br}_2$ | (4) $\text{C}_2\text{H}_2\text{Br} + \text{Br}_2 = \text{C}_2\text{H}_2\text{Br}_2 + \text{Br}$ |
| (5) $\text{C}_2\text{H}_2\text{Br} + \text{Br}_2 = \text{C}_2\text{H}_2\text{Br}_2 + \text{Br}$ | (5) $\text{Br} + \text{Wall} = \frac{1}{2}\text{Br}_2$ |
| (6) $\text{C}_2\text{H}_2\text{Br} = \text{C}_2\text{H}_2 + \text{Br}$ | |
| (7) $\text{Br}_3 + \text{Wall} = \frac{3}{2}\text{Br}_2$ | |
| (7') $\text{C}_2\text{H}_2\text{Br}_3 + \text{Wall} = \text{C}_2\text{H}_2 + \frac{3}{2}\text{Br}_2 \text{ or } \text{C}_2\text{H}_2\text{Br}_2 + \frac{1}{2}\text{Br}_2$ | |

²⁵⁹ Straus, Kollek, and Heyn, *Ber.*, **63**, 1868 (1930).

²⁶⁰ Straus, Kollek, and Hauptmann, *Ber.*, **63**, 1886 (1930).

²⁶¹ Peters and Neumann, *Angew. Chem.*, **45**, 261 (1932).

²⁶² Müller and Schumacher, *Z. physik. Chem.*, **B39**, 352 (1938).

²⁶³ Franke and Schumacher, *ibid.*, **B34**, 181 (1936).

The halogens are added to alkynes in the presence of metals and metallic salts. The reaction of chlorine and ethyne is explosive if not modified in some way, and metallic catalysts offer a suitable means of effecting such control. One successful method of modification involved the use of antimony pentachloride in place of chlorine as halogenating agent.²⁶⁴ The reaction using chlorine as halogen-containing agent may be modified by catalysts. Aluminum, iron, or an alloy of aluminum, silica, and iron was successfully used in the preparation of tetrachloroethane.²⁶⁵

In hydrogen bromide addition, the same effect of peroxide catalysis observed in the case of alkenes persists with alkynes. In the presence of peroxides, propyne added hydrogen bromide to form 1,2-dibromopropane, whereas under antioxidant conditions or without added peroxides the product was 2,2-dibromopropane.²⁶⁶

Metals and metallic salts catalyze the addition of hydrogen halides to alkynes. Addition of hydrogen chloride to ethyne in the gaseous phase seems to occur only in the presence of metallic chlorides.²⁶⁷ Bismuth chloride and mercuric chloride accelerate this reaction.^{267, 268} Tetrachloroethane was produced in good yield when iron, iron oxides, or antimony pentachloride was used.²⁶⁹ Cupric chloride in combination with ammonium chloride has also been used as catalyst but the results were comparatively poor.²⁷⁰

Mercuric bromide, antimony bromide, or ferric bromide on asbestos, and ferric bromide or bismuth bromide on pumice were used as catalysts in hydrogen bromide addition to ethyne.²⁷¹ Ferric bromide on pumice and mercuric or antimony bromide on asbestos were effective. Cupric chloride with ammonium chloride or the corresponding bromides also acted as catalysts.²⁷²

VII. NITRATION OF ALIPHATIC HYDROCARBONS

Nitration of aliphatics during the past five years has emerged from the status of purely laboratory chemistry to become an industry of

²⁶⁴ Langguth, *Chimie & industrie*, **25**, 22 (1931).

²⁶⁵ Fukagawa, *Proc. World Eng. Congr. Tokyo*, **31**, 387 (1929) [*C. A.*, **25**, 5660 (1931)].

²⁶⁶ Kharasch, McNab, and McNab, *J. Am. Chem. Soc.*, **57**, 2463 (1935).

²⁶⁷ Wibaut and Van Dalfsen, *Rec. trav. chim.*, **51**, 636 (1932).

²⁶⁸ Van Dalfsen and Wibaut, *ibid.*, **53**, 489 (1934).

²⁶⁹ Valiaschko and Kosenko, *Ukrain. Chem. J.*, **7**, 12 (1932) [*Brit. Chem. Abstracts*, [A] **47** (1933)].

²⁷⁰ Arutyunyan and Marutyan, *Caoutchouc and Rubber (U.S.S.R.)*, No. 2, 36 (1937) [*C. A.*, **31**, 6189 (1937)].

²⁷¹ Wibaut, *Rec. trav. chim.*, **50**, 313 (1931).

²⁷² Kozlov, *J. Applied Chem. (U.S.S.R.)*, **10**, 116 (1937) [*C. A.*, **31**, 4263 (1937)].

national importance, providing new explosives, emulsifying agents, and solvents. Hass and co-workers opened this field when they demonstrated that the reaction of nitric acid with ethane, propane, the butanes, and the pentanes was clear cut and the nitration products were nitromethanes, nitroethanes, and higher nitroparaffins.

Of the aliphatic hydrocarbons the alkanes are the most difficult to nitrate. The lower alkanes presented the greatest problem, which has been solved by the use of vapor-phase nitration. In general the order of nitration is: primary < secondary < tertiary, although high temperatures increase the yield of primary at the expense of the secondary and tertiary. Superatmospheric pressure increases the rate of reaction. Mono- and dinitro compounds are the principal products from alkanes, and the mononitro compounds are best produced in vapor phase with nitric acid. Either the nitric or nitrosulfuric acid liquid-phase reactions or the nitrogen tetroxide vapor-phase reaction produces a mixture of mono- and dinitro products. In the liquid phase the formation of the mononitro compound is promoted by the use of a dilute acid.

Nitroso, nitro, nitrite, and nitrate groups add to alkenes in various combinations. The course of the reaction with nitrogen oxides seems to be affected by the relative polarities of the unsaturated carbon atoms. Substitution products have been found, but they may be formed by addition followed by the splitting out of a simple molecule. The mechanism of the reaction with alkenes is addition to the double bond of the two component parts of the reagent, either with or without subsequent oxidation. Complex alicyclic products containing nitrogen in the ring are formed from alkynes.

Nitration of Alkanes

Vapor Phase with Nitric Acid. In vapor-phase nitration of alkanes by nitric acid, a homogeneous gas-phase reaction occurs²⁷³ which is presumably of second order.²⁷⁴ Oxidation is the chief reaction competing with nitration.

Vapor-phase nitration has been utilized, especially for the lower alkanes, since those having fewer than five carbon atoms have critical temperatures below the temperatures at which sufficiently rapid nitration occurs.²⁷⁴ Mononitroalkanes can be produced by vapor-phase nitration practically to the exclusion of dinitro and more highly nitrated compounds by means of short contact time. In the nitration of pentane at 400°, all theoretically possible mononitro compounds which

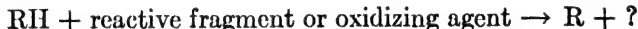
²⁷³ Hibshman, Pierson, and Hass, *Ind. Eng. Chem.*, **32**, 427 (1940).

²⁷⁴ Hass, Hodge, and Vanderbilt, *ibid.*, **28**, 339 (1936).

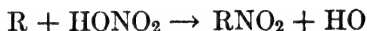
could result from fission of a C—H or C—C bond were formed.²⁷⁵ Although the presence of free radicals was not actually established, the data are highly indicative of a free-radical mechanism.

Although the ease of replacement of a hydrogen atom by a nitro group follows the scheme: tertiary > secondary > primary, the ratio of the various nitro compounds formed can be partly controlled by temperature and pressure variations. As the temperature rises the yield of primary derivatives increases, and that of the secondary and tertiary decreases.²⁷⁴ The variation in yield may be due to a change in the relative reaction rates of primary and secondary carbon atoms with increased temperature.²⁷⁶ The reaction may be less selective and the primary compound more stable at the higher temperature.²⁷⁴

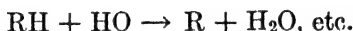
In all cases tried, McCleary and Degering found, besides the nitro products, all the alkenes predicted by the free-radical theory of Rice for thermal decomposition of alkanes.^{276, 277} The expected variation of the quantity of alkenes and nitro products with change in concentration of the nitric acid was likewise obtained.²⁷⁶ The mononitro compounds accounted for by a free-radical mechanism were found by other investigators.²⁷⁴ McCleary and Degering have suggested the following mechanism to account for all the products of vapor-phase nitration:



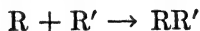
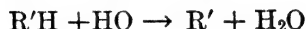
then



and



$R \rightarrow \text{olefin} + R'$ (where R' is a free radical of lower molecular weight than R)



The paraffin may also be oxidized to carbon dioxide and water or to some oxidized intermediate.

Vapor Phase with Nitrogen Tetroxide. Vapor-phase nitrations have been carried out with nitrogen tetroxide on alkanes from methane to nonane, with the exception of ethane and butane. The optimum temperature was about 200°.²⁷⁸

²⁷⁵ Hass and Patterson, *ibid.*, **30**, 67 (1938).

²⁷⁶ McCleary and Degering, *ibid.*, **30**, 64 (1938).

²⁷⁷ Rice, *J. Am. Chem. Soc.*, **53**, 1959 (1931).

²⁷⁸ Urbanski and Slon, *II^e Congr. Mondial Petrole*, **2**, Sect. 2, Phys. Chem. raffinage 163 (1937).

Liquid Phase with Nitric Acid and Nitric-Sulfuric Acid Mixtures.

Nitration in the liquid phase, although unsuitable for lower homologs, has been applied to alkanes of five or more carbon atoms using nitric acid or mixtures of nitric and sulfuric acids. Increased concentration of acid increases both oxidation and nitration and produces a relatively greater amount of di- and polynitro derivatives. More elevated temperatures and longer time factors produce higher yields of the dinitro product.²⁷⁹ Branched-chain compounds containing tertiary carbon atoms are more readily nitrated than the normal compounds, but a quaternary hydrocarbon compares with the normal series in lack of reactivity to nitric acid.²⁸⁰

A mixture of nitric and sulfuric acids has frequently been used for nitration. The sulfuric acid has been regarded merely as an agent to remove the water formed by the nitration reaction. The action of the mixture, however, is quite different from that of concentrated nitric acid. Markovnikov obtained evidence that such a mixture contains

nitrosulfuric acid, $\text{SO}_2 \begin{array}{l} \text{OH} \\ \diagup \\ \text{ONO}_2 \end{array}$, which is the active agent.²⁸¹ Volatile

alkanes have been distilled over nitric-sulfuric acid mixtures without undergoing much reaction, although higher-boiling normal alkanes reacted near their boiling points.^{282, 283} The acid mixture had little action on tertiary hydrocarbons a few degrees above zero in contrast to the action of nitric acid.²⁸³

In liquid-phase as in vapor-phase nitration of the lower alkanes, the branched-chain alkanes are more reactive than the normal compounds. Isopentane, isohexane, and isoheptane with nitric acid produce trinitro compounds.^{284, 285} Alkanes of the type R_2CHCHR_2 (where R is any normal alkyl group) react readily with fuming acid.²⁸³ Higher temperatures are necessary when a more dilute acid is used.^{282, 286} A slight variation in pressure has no effect.²⁷⁹ Increased concentration of acid causes decreased production of tertiary derivatives and increased production of

²⁷⁹ Konovalov, *J. Russ. Phys. Chem. Soc.*, **31**, 57 (1899); *J. Chem. Soc.*, **76**, [1] 844 (1899) [*Chem. Zentr.*, **70**, I, 1063 (1899)].

²⁸⁰ Markovnikov, *J. Russ. Phys. Chem. Soc.*, **31**, 523 (1899) [*Chem. Zentr.*, **70**, II, 473 (1899)].

²⁸¹ Markovnikov, *J. prakt. Chem.*, [2] **59**, 556 (1899).

²⁸² Worstall, *Am. Chem. J.*, **20**, 202 (1898).

²⁸³ Markovnikov, *Ber.*, **32**, 1441 (1899).

²⁸⁴ Poni and Costachescu, *Ann. sci. univ. Jassy*, **2**, 119 (1903); *J. Chem. Soc.*, **84**, [1] 596 (1903).

²⁸⁵ Francis and Young, *J. Chem. Soc.*, **73**, 928 (1898).

²⁸⁶ Markovnikov, *J. Russ. Phys. Chem. Soc.*, **31**, 47 (1899) [*Chem. Zentr.*, **70**, I, 1064 (1899)].

secondary and especially primary derivatives.²⁸⁷ The primary derivative was practically the only nitro product formed in some cases from the concentrated nitric acid.

The mechanism of nitration apparently involves removal of hydrogen as an atom rather than as a proton or negative ion.²⁸⁸ The acceptor-donor inversion mechanism seems most plausible since it is supported by the greater substitutive reactivity of tertiary carbon atoms, the electron repulsion of tertiary groups, and the absence of rearrangement.

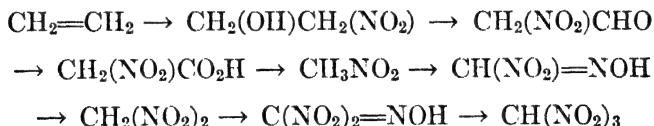
Catalytic Nitration of Alkanes. Alkanes react with nitric oxide at high temperatures in the presence of a catalyst.²⁸⁹ Methane reacted with nitric oxide in the presence of a catalyst to give hydrocyanic acid.²⁹⁰ The reaction began around 900°, and the yield increased with temperature.

Nitration of Alkenes

Nitric Acid. Concentrated or fuming nitric acid reacts with alkenes to form both nitration and oxidation products such as nitroalkanes, nitroalkenes, and nitro-nitric esters. Low temperatures and dilution with an inert solvent reduce secondary reactions by inhibiting oxidation and formation of nitrous reagents.²⁹¹

Wieland postulated a mechanism for the action of nitric acid on alkenes.^{292, 293} He assumed that it adds not as an electrolyte, but as HO—NO₂. The production of 2-methyl-3-nitro-2-butene and the nitric ester of 2-methyl-3-nitrobutan-2-ol from 2-methyl-2-butene was evidence of the addition as HO—NO₂.

Other evidence supporting the addition of nitric acid as HO—NO₂ is the isolation of 2-nitroethan-1-ol as a reaction product from the passage of ethene into fuming nitric acid.²⁹⁴



The work of Michael and Carlson, however, indicates that nitric acid adds as H—ONO₂ rather than as HO—NO₂.²⁹¹ Nitration has been

²⁸⁷ Konovalov, *J. Russ. Phys. Chem. Soc.*, **38**, I, 109, 124 (1906); *J. Chem. Soc.*, **92**, [1] 1 (1907) [*Chem. Zentr.*, **78**, I, 400 (1907)].

²⁸⁸ Stevens and Schiessler, *J. Am. Chem. Soc.*, **62**, 2885 (1940).

²⁸⁹ Platonov and Shaikind, *J. Gen. Chem. (U.S.S.R.)*, **4**, 434 (1934) [*C. A.*, **29**, 1769 (1935)].

²⁹⁰ Elod and Nedelmann, *Z. Elektrochem.*, **33**, 217 (1927).

²⁹¹ Michael and Carlson, *J. Am. Chem. Soc.*, **57**, 1268 (1935).

²⁹² Wieland and Rahn, *Ber.*, **54**, 1770 (1921).

²⁹³ Wieland and Sakellarios, *Ber.*, **53**, 201 (1920).

²⁹⁴ McKie, *J. Chem. Soc.*, 962 (1927).

accomplished indirectly in various cases by nitrous gases formed from oxidative side reactions. A mechanism involving addition of nitrogen tetroxide to the double bond as the first step has been offered to account for some of Wieland's products. The formation of the nitric ester of 2-nitroethan-1-ol from ethene, already cited, was accomplished by a mixture of nitric and sulfuric acids rather than by nitric acid.²⁹³ The reactive agent in such a mixture, the mixed anhydride $\text{HOSO}_2\text{ONO}_2$ instead of nitric acid,²⁸² should lead to the formation of the sulfuric ester of 2-nitroethan-1-ol, and the nitro-nitric ester would result from the nitric ester radical replacement of the less negative sulfuric ester group.

Nitrogen Oxides. Addition of nitrogen oxides is not always predictable because of the ability of the oxide molecule to rupture at different points, and the capacity of the oxides to function as polymerizing and oxidizing agents. Since nitroso, nitro, nitrite, and nitrate groups may result from nitrogen oxides, a number of combinations is possible. The type of product appears to be partly determined by the relative polarities of the unsaturated carbons.²⁹⁵ The addition of nitrogen oxides to alkenes is complex because of the diverse capacities in which these oxides can function. A prediction of the products might be expected by consideration of the relative polarities of the unsaturated carbons and of the groups which arise from the intramolecular scission of the oxide.

The products identified from 2-methyl-2-butene and pure nitrogen tetroxide were the dimeric nitroso-nitric ester, the dinitro compound, and a nitroalkene.^{295, 296} The course of the reaction depends mostly on the polarities of the unsaturated carbon atoms and very little on the proportions in which the components are present in the equilibrium:²⁹⁵ $2\text{NO}_2 \rightleftharpoons \text{O}_2\text{N}-\text{ONO}$.

Alkenes of the formula $\text{RR}'\text{C}=\text{CHR}''$ and $\text{RR}'\text{C}=\text{CR}''\text{R}'''$ reacted readily to form nitrosyl chloride addition products, but those of the type $\text{RCH}=\text{CHR}'$ reacted in this manner only with difficulty.²⁹⁷ The types having a hydrogen atom on one or more of the unsaturated carbons can form the oximes, $\text{RCHClC}(=\text{NOH})\text{R}'$ or $\text{RR}'\text{CClC}(=\text{NOH})\text{R}''$, by migration of a hydrogen atom.

Catalytic Nitration of Alkenes. Nitric oxide reacts with ethene at high temperature in the presence of a catalyst to produce hydrocyanic acid, ammonia, and products of decomposition, oxidation, and polymerization.²⁹⁰ A mixture of alumina and quartz was the most effective catalyst. Yields of hydrocyanic acid increase with the proportion of ethene in the mixture and with the reaction temperature to 1000° , at

²⁹⁵ Michael and Carlson, *J. Am. Chem. Soc.*, **59**, 843 (1937).

²⁹⁶ Michael and Carlson, *J. Org. Chem.*, **4**, 169 (1939).

²⁹⁷ Tuot, *Compt. rend.*, **204**, 697 (1937).

which point both decomposition and polymerization of the ethene take place rapidly. The initial step in the production of hydrocyanic acid is probably the formation of ammonia by the reduction of nitric oxide. The ammonia then reacts on ethene or one of the unsaturated intermediate products of the decomposition of ethene to produce hydrocyanic acid.

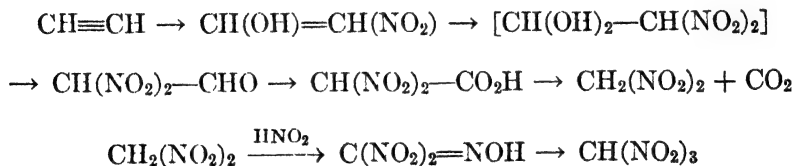
Electrochemical Nitration of Alkenes. Alkenes can be nitrated electrolytically.²⁹⁸ Electrolysis of acetone solutions of nitrates or nitric acid and ethene resulted in the addition of nitrate and condensation. Increase in current density favors ester formation since this increase causes higher concentration of nitrate. Ester formation is favored by anode material which gives a higher overvoltage and by dilution of the ethene with an inert gas.

Nitration of Alkynes

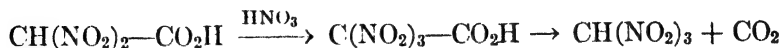
The nitration of ethyne yields complex nitrogenous compounds in addition to trinitromethane. Oxidation also takes place, and the products undergo secondary reactions.²⁹⁹ Fuming nitric acid and nitric-sulfuric acid mixtures are used as reagents.

As catalysts, chloroplatinic acid and the nitrates of silver, uranium, and copper were ineffective in increasing the yield of trinitromethane, but mercuric nitrate was effective.³⁰⁰ Chloroplatinic acid and silver and uranium nitrates favored oxidation.

McKie accounts for the production of trinitromethane by the following reaction:²⁹⁴



The latter part of this mechanism may be instead:³⁰⁰



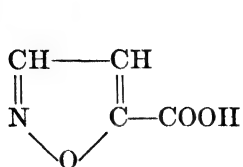
Complex products from the passage of ethyne into cold fuming nitric acid have been identified and each contains one or more isoxazole nuclei. These products are α -isoxazolecarboxylic acid, α,β' -diisoxazolyl ketone,

²⁹⁸ Ohman, *Z. Elektrochem.*, **42**, 862 (1936).

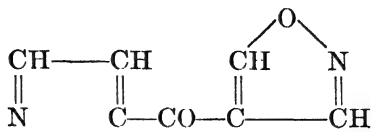
²⁹⁹ Quilico and Freri, *Gazz. chim. ital.*, **59**, 930 (1929).

³⁰⁰ Orton and McKie, *J. Chem. Soc.*, **117**, 283 (1920).

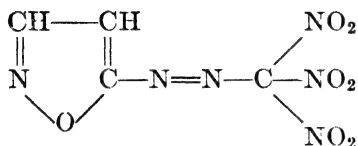
α -isoxazoleazotrinitromethane, and a small quantity of α,α' -diisoxazolyfuroxan.^{299, 301, 302, 303, 304}



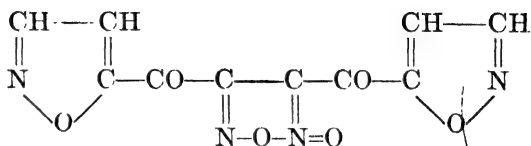
α -Isoxazolecarboxylic acid



α,β' -Diisoxazoly ketone



α -Isoxazoleazotrinitromethane



α,α' -Diisoxazolyfuroxan

Ethyne reacts also with nitric oxide at high temperatures in the presence of a catalyst to produce hydrocyanic acid. A slightly higher yield was obtained than from ethene under the same conditions, but more polymerization products and formaldehyde were obtained.

VIII. OXIDATION OF ALIPHATIC HYDROCARBONS

The oxidation of aliphatic hydrocarbons has been widely studied in order to establish an adequate reaction mechanism. Four theories of oxidation reactions exist: hydroxylation, peroxidation, aldehyde degradation, and activation of molecules. Chain propagation is agreed upon in all theories. Oxidation reactions are characterized by induction periods and are sensitized by the addition of intermediate oxidation products. An excess of oxygen has an inhibitory effect on the oxidation of both saturated and unsaturated aliphatics. Alkane oxidations occur at lower temperatures than are necessary for alkene-oxygen reactions. Hydrocarbon-oxygen reaction rates are increased by increasing the pressure, although alkanes are more affected by pressure changes than alkenes. The rate of reaction increases with length of the hydrocarbon chain and is greater for straight-chain compounds than for branched-chain isomers.

Both saturated and unsaturated aliphatics have been oxidized in the presence of nitrogen oxides, metals, and metallic oxides. Partial oxidation of aliphatics has been carried out with such compounds as ozone, metallic oxides, acids, and hydrogen peroxide. Alkene and alkyne hydrations have been carried out with acids, salts, and metallic oxide catalysts.

²⁹¹ Quilico and Freri, *Gazz. chim. ital.*, **60**, 172 (1930).

²⁹² Quilico, *ibid.*, **61**, 265 (1931).

²⁹³ Quilico, *ibid.*, **62**, 503 (1932).

²⁹⁴ Quilico and Freri, *ibid.*, **62**, 436 (1932).

Oxidation of Alkanes

The early theories of preferential oxidation of carbon or hydrogen have given place to the more complex hydroxylation and peroxidation theories.

Thermal Oxidation of Alkanes. A study of molecular structure and its effect on thermal oxidation of alkanes leads to the following generalizations: (1) as the length of normal hydrocarbon chains is increased, less difficulty in oxidation is noted;³⁰⁵ (2) branching and condensation of the molecule increase the difficulty of oxidation.³⁰⁶

Temperatures between 0° and 700° have been used in thermal reactions, but most of the work has been carried out in the range between 200° and 500°. An increase of temperature usually results in a shorter induction period and a more rapid rate of oxidation.^{307, 308} Elevation of temperature to just below that at which cracking is ordinarily carried out causes rupture of molecules.³⁰⁹

Pressure increase influences hydrocarbon oxidation in several ways:³¹⁰ (a) it increases frequency of molecular collisions with subsequent increase in reaction rate; (b) it deactivates chain carriers; (c) it alters the electrostatic field, giving rise to induced or increased polarity; and (d) it directs a reaction so that less space is required.

Alkane oxidations may be sensitized or inhibited by foreign gases and solids and by the addition of intermediate reaction products. In general, the induction period is shortened and the rate of the main reaction increased by addition of intermediate oxidation products, such as alcohols, aldehydes, and acids.^{311, 312, 313, 314} Oxides of carbon have little effect in most instances.³¹⁵ The influence of hydrocarbon halides, hydrocarbons, and nitrogen diluents depends largely on other experimental conditions.^{313, 316, 317, 318, 319, 320, 321} Acceleration by diluents may

³⁰⁵ Lewis, *J. Chem. Soc.*, 1555 (1927).

³⁰⁶ Maman, *Compt. rend.*, **205**, 319 (1937).

³⁰⁷ Arditti, *ibid.*, **201**, 396 (1935).

³⁰⁸ Wheeler and Blair, *J. Soc. Chem. Ind.*, **42**, 491T (1923).

³⁰⁹ Burwell, *Ind. Eng. Chem.*, **26**, 204 (1934).

³¹⁰ Newitt, *Chem. Rev.*, **21**, 299 (1937).

³¹¹ Bone and Gardner, *Proc. Roy. Soc. (London)*, **154A**, 297 (1936).

³¹² Bone and Allum, *ibid.*, **134A**, 578 (1932).

³¹³ Pease, *Chem. Rev.*, **21**, 279 (1937).

³¹⁴ Pidgeon and Egerton, *J. Chem. Soc.*, 676 (1932).

³¹⁵ Norrish and Foord, *Proc. Roy. Soc. (London)*, **157A**, 503 (1936).

³¹⁶ Prettre, *Ann. combustibles liquides*, **12**, 411 (1937).

³¹⁷ Van Heiningen, *Rec. trav. chim.*, **55**, 65 (1936).

³¹⁸ Coward, *J. Chem. Soc.*, 1382 (1934).

³¹⁹ Jorissen, Booy, and Van Heiningen, *Rec. trav. chim.*, **51**, 868 (1932).

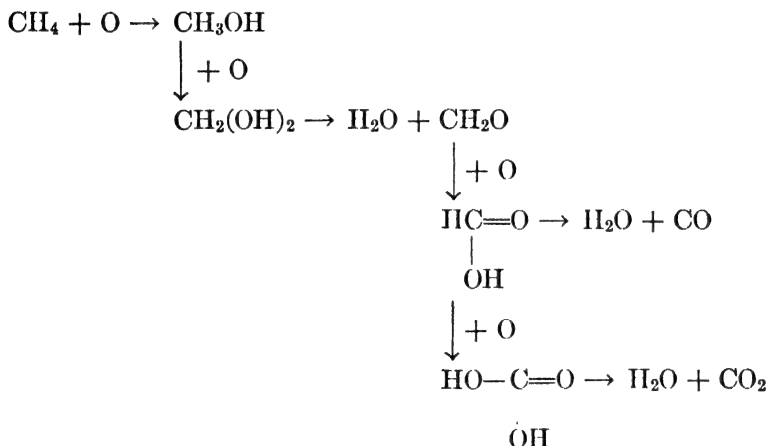
³²⁰ Jorissen and Hermans, *ibid.*, **52**, 271 (1933).

³²¹ Steacie and Plewes, *Proc. Roy. Soc. (London)*, **146A**, 583 (1934).

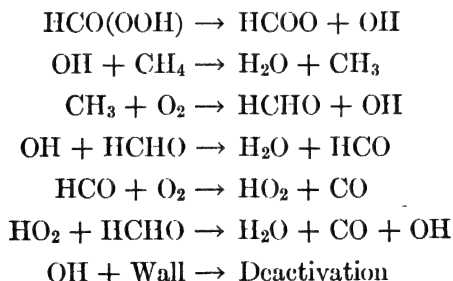
be attributed to prevention of chain breaking at the walls; inhibition may be the result of chain breaking by collision with the diluent.

An induction period is noted for all alkane oxidations, and it is, therefore, highly probable that a chain reaction occurs.^{313, 322} During the induction period, active centers are formed, and the reaction chains are initiated from these centers.³¹¹ Monovalent radicals may be formed at the walls, and the reaction is slower when the reactor is coated with material destroying or preventing radical formation.³²³

The hydroxylation theory of alkane-oxygen reactions postulates the formation of an alcohol as the primary step in hydrocarbon oxidation.³²⁴ Hydroxylated molecules then react according to the following scheme shown for methane:



The formation of the intermediate compounds, formaldehyde and formic acid, has also been explained by the peroxidation theory of von Elbe and Lewis.³²⁵ The initial product, a peracid, decomposes at the surfaces to give monovalent radicals which carry on the reaction:



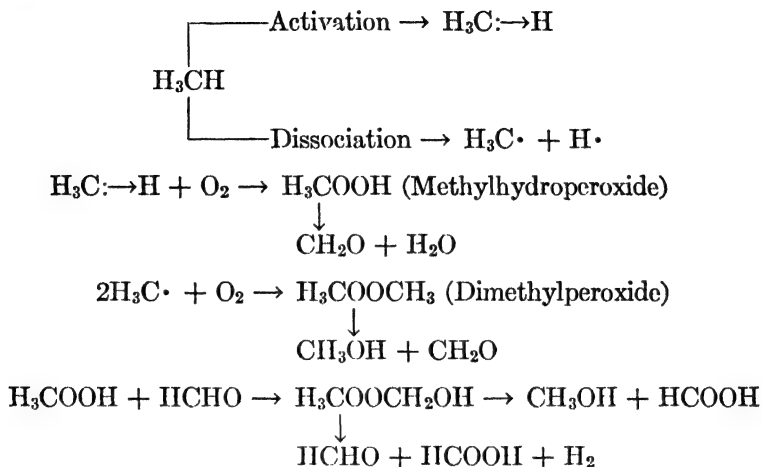
³²² Bone and Hill, *ibid.*, **129A**, 434 (1930).

³²³ Lewis and von Elbe, "Combustion, Flames, and Explosions of Gases," Cambridge University (1938), pp. 89, 110.

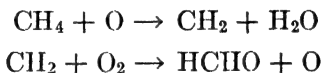
³²⁴ Bone, *J. Chem. Soc.*, 1599 (1933).

³²⁵ von Elbe and Lewis, *J. Am. Chem. Soc.*, **59**, 976 (1937).

Milas has accounted for the methane oxidation through the formation of peroxides arising from activated molecules.³²⁶



A mechanism involving the formation of formaldehyde from free hydrocarbons has been suggested:³²⁷



The formaldehyde is further oxidized to formic acid and subsequently to carbon dioxide and water. An unstable oxygenated molecule CH_4O may possibly be formed and decomposed into alcohol and aldehyde. This suggestion links the peroxidation and hydroxylation theories.

Another theory based upon primary dehydrogenation indicates the following reactions:³²⁸

1. Primary dehydrogenation to unsaturated hydrocarbons.
2. Combination of the unsaturated hydrocarbon with oxygen to form unstable peroxides.
3. Decomposition of peroxides and oxidation of the products formed to carbon monoxide, carbon dioxide, and water. If large quantities of alkenes are present, their formation may be due to stabilization of a by-product rather than to an initial reaction.³²⁹

According to the theory of aldehyde degradation for higher alkanes, the initial oxidation product is an aldehyde with the same number of carbon atoms as the original alkane.³³⁰ The aldehyde is further oxidized with the loss of one carbon atom. This process is repeated until prod-

³²⁶ Milas, *Chem. Rev.*, **10**, 295 (1932).

³²⁷ Norrish, *Proc. Roy. Soc. (London)*, **150A**, 36 (1935).

³²⁸ Lewis, *J. Chem. Soc.*, 759 (1929).

³²⁹ Ubbelohde, *Proc. Roy. Soc. (London)*, **152A**, 354, 378 (1935).

³³⁰ Pope, Dykstra, and Edgar, *J. Am. Chem. Soc.*, **51**, 1875 (1929).

ucts are formed which are resistant to further oxidation or a temperature is reached at which general decomposition of the molecule takes place. The point of initial oxidation is on the carbon at the end of the longest unbranched chain.^{308, 330} In the case of branched molecules, the reaction rate decreases when the branch is reached. The slower reaction rate results from the formation at the branch of a ketone, which is more resistant to oxidation than an aldehyde. Chain propagation of the reaction is common to all the theories discussed, i.e., hydroxylation, peroxidation, activation of the molecules and formation of free radicals, and aldehyde degradation.

Catalytic Oxidation of Alkanes. Alkane oxidation may be catalyzed by nitrogen oxides and metals.^{318, 331} The pronounced effect of nitrogen peroxide is probably related to the ease with which the valence of nitrogen may be changed,³³² although initial combination of the hydrocarbon and nitrogen peroxide may occur.^{333, 334} In the case of methane, this unstable complex would decompose to formaldehyde and a nitrogen oxide. Methyl nitrite has been used as a promoter in the oxidation of methane and ethane.³³⁵

Some metallic catalysts promote alkane oxidation so that equilibrium is reached almost instantly. Platinum, silver, copper, palladium, and manganese vanadate may be used satisfactorily under certain conditions.^{336, 337, 338}

Use of Oxidants Other than Oxygen Gas. Metallic oxides may become oxygen donors in oxidation reactions with or without catalysts. Copper oxide was found to be the most effective oxidizing agent; oxides of iron, tin, zinc, and cobalt were less effective.^{339, 340} The reaction of ethane with selenium oxide was slow and incomplete, resulting in the formation of glyoxal, acetic acid, and carbon dioxide.³⁴¹

When catalysts were used with cupric oxide and methane, their efficiency in the reaction occurred in the following order: cuprous chloride,^{339, 342, 343} cobaltous oxide,^{339, 343} manganese dioxide.³⁴⁰ Ferric ox-

³³¹ Gimmelman, Neumann, and Sokoff, *Acta Physicochim. U.R.S.S.*, **5**, 903 (1936).

³³² Layng and Soukup, *Ind. Eng. Chem.*, **20**, 1052 (1928).

³³³ Serbinov and Nieman, *Compt. rend. U.R.S.S.*, **2**, 297 (1934) [*C. A.*, **28**, 5320 (1934)].

³³⁴ Smith and Milner, *Ind. Eng. Chem.*, **23**, 357 (1931).

³³⁵ Gimmelman and Neumann, *Acta Physicochim. U.R.S.S.*, **7**, 221 (1937).

³³⁶ Davies, *Phil. Mag.*, **21**, 513 (1936).

³³⁷ Boomer and Broughton, *Can. J. Research*, **15B**, 375 (1937); Boomer and Thomas *ibid.*, **15B**, 401, 414 (1937).

³³⁸ Reyerson and Swearingen, *J. Phys. Chem.*, **32**, 192 (1928).

³³⁹ Campbell and Gray, *J. Soc. Chem. Ind.*, **49**, 450T (1930).

³⁴⁰ Neumann and Wang, *Angew. Chem.*, **46**, 57 (1933).

³⁴¹ Riley and Friend, *J. Chem. Soc.*, 2342 (1932).

³⁴² Campbell and Gray, *J. Soc. Chem. Ind.*, **49**, 447T (1930).

³⁴³ Arneil, *ibid.*, **53**, 89T (1934).

ide,^{340, 343} ceric oxide,³⁴³ chromic oxide, molybdic trioxide, and a uranium oxide, U_3O_8 , were also used as catalysts in methane oxidations. Lead chromate³³⁹ as an oxidizing agent yields carbon monoxide from methane.

Perchloric acid has been used with methane, ethane, and heptane. The resulting compounds were products of incomplete oxidation, and much carbon monoxide was formed.³⁴⁴

Oxidation of Alkenes

Oxidation reactions of the lower alkenes indicate that the hydroxylation and peroxidation theories for alkanes also apply to alkenes. Cyclic oxides form readily at points of unsaturation. Chain propagation of alkene oxidation is evidenced by an induction period,³⁴⁵ the inhibitory effect of excess oxygen,³⁴⁶ and the retardation due to increased surfaces. Uncatalyzed alcohol formation from alkenes is a reversible reaction in which the equilibrium is well over on the alkene side.³⁴⁷ The reaction is most favorable for ethene, and increasingly small yields are obtained as higher alkenes are used.

Nitric oxide and metallic salts and oxides have been used to catalyze the oxidation of alkenes. Catalytic hydration of alkenes produces alcohols, but equilibrium conditions are, in general, unfavorable for this reaction. Ozone, hydrogen peroxide, selenium oxide, potassium permanganate, and peracetic acid have also been used to oxidize alkenes. The point of initial oxidation with different oxidants varies with the structures of the alkenes.

Thermal Oxidation of Alkenes. Thermal oxidation reactions of the 1-alkenes in the vapor phase are less intense than those of the corresponding alkanes. Thermal decomposition occurred at high temperatures in the presence of oxygen but at a much slower rate than oxidation.³⁴⁸ At temperatures above 500° polymerization became a dominant factor even when diluents were used.³⁴⁹

Ethene oxidations yield aldehydes and unsaturated alcohols previous to the formation of any oxides or peroxides,³²⁴ although in one case ethene oxide³⁴⁹ was reported as an initial product. Propene and isobutene reacted much more rapidly with oxygen than did ethene.³⁴⁸ Oxidation of the heptenes indicates that the initial action of oxygen is on a non-terminal saturated carbon atom.³⁵⁰ Oxidation of *n*-octene, except

³⁴⁴ Vialard-Goudou, *Compt. rend.*, **203**, 565 (1936).

³⁴⁵ Thompson and Hinshelwood, *Proc. Roy. Soc. (London)*, **125A**, 277 (1929).

³⁴⁶ Bone, Haffner, and Rance, *ibid.*, **143A**, 16 (1933).

³⁴⁷ Stanley, Youell, and Dymock, *J. Soc. Chem. Ind.*, **53**, 205T (1934).

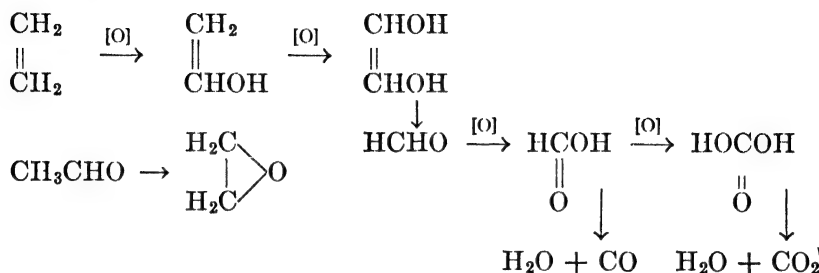
³⁴⁸ Dairs, *Ind. Eng. Chem.*, **20**, 1055 (1928).

³⁴⁹ Lenher, *J. Am. Chem. Soc.*, **53**, 2420 (1931).

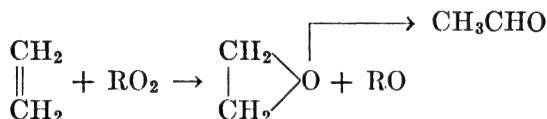
³⁵⁰ Beatty and Edgar, *ibid.*, **56**, 107 (1934).

for a higher reaction temperature, was similar to that of *n*-octane,³³⁰ and indicated that the octene reaction began not at the point of unsaturation but at the opposite end of the molecule.

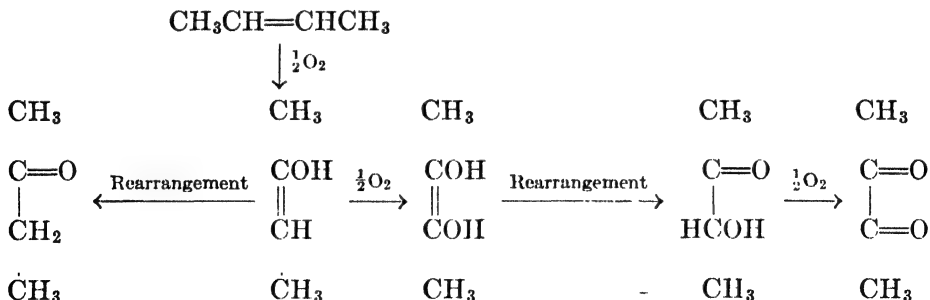
The hydroxylation theory advanced for saturated hydrocarbons was also applied to alkenes:³²⁴



According to the peroxidation theory, the primary reaction of ethene and oxygen yields a peroxide which reacts further with the alkene to produce alkene oxides. The unstable oxide decomposes to acetaldehyde, and complete oxidation of the aldehyde follows:

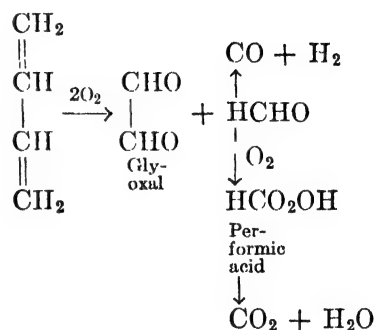
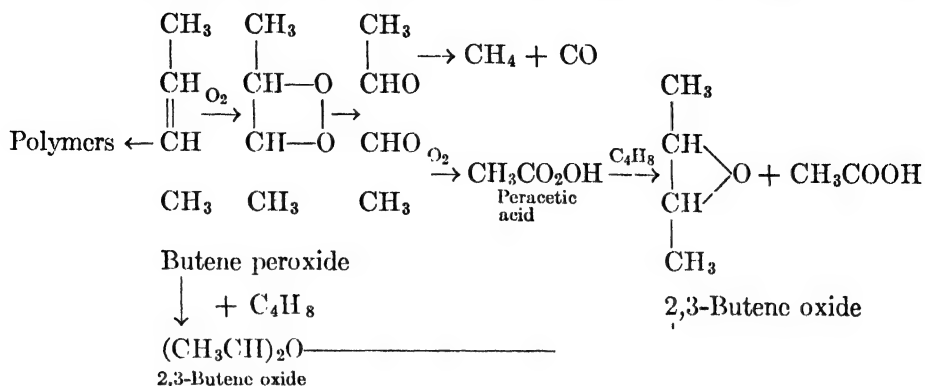


Oxidation of 2-butene indicated the probability of peroxidation as the primary reaction.³⁵¹ If hydroxylation predominates, the following scheme explains the reaction:



Such ketone formation was not substantiated by experimental evidence. The acetaldehyde, butadiene, alkene oxide, acids, glyoxal, and water found in the 2-butene oxidation products are, however, accounted for by a mechanism in which peroxidation is the primary reaction.

³⁵¹ Lucas, Prater, and Morris, *ibid.*, **57**, 723 (1935).



Catalytic Oxidation and Hydration of Alkenes. Oxidation of alkenes to intermediate products has been carried out in the presence of catalysts. Addition of nitric oxide to ethene-oxygen reaction mixtures eliminated the induction period and shortened the reaction period.³⁴⁶ Ether accelerated propene oxidation.³⁵² Cobaltous oleate, manganese vanadate, and vanadium pentoxides function as catalysts.^{353, 354, 355}

Catalytic hydration of the alkenes has not been entirely successful since most catalysts become effective only at temperatures high enough to displace the equilibrium toward the alkenes.³⁵⁶ Cadmium metaphosphate was used in the hydration of ethene at atmospheric pressure.³⁵⁷ Alumina and tungstic oxide catalysts were also used, and the products included acetic acid and polymerization products.³⁵⁸ 2-Butene has been hydrated in the presence of cuprous chloride, thoria, and phosphoric acid.³⁵⁹ 2-Methyl-1-propene and 2-methyl-2-butene were hydrated in

³⁵² Townend, *Chem. Rev.*, **21**, 259 (1937).

³⁵³ Hyman and Wagner, *J. Am. Chem. Soc.*, **52**, 4345 (1930).

³⁵⁴ Wilken-Jorden, *J. Chem. Met. Mining Soc. S. Africa*, **32**, 283 (1932).

³⁵⁵ Faith and Dendurent, *Refiner Natural Gasoline Mfr.*, **18**, 393 (1939).

³⁵⁶ Shiffler, Holm, and Brooke, *Ind. Eng. Chem.*, **31**, 1099 (1939).

³⁵⁷ Appleby, Glass, and Horsley, *J. Soc. Chem. Ind.*, **56**, 279 (1937).

³⁵⁸ Bliss and Dodge, *Ind. Eng. Chem.*, **29**, 19 (1937).

³⁵⁹ Marek and Fledge, *ibid.*, **24**, 1428 (1932).

the presence of potassium nitrate and nitric acid.^{360, 361} Other acids were used with 2-methyl-2-butene, and the order of the catalytic influence of 0.1 molar solutions was: dithionic>sulfuric>hydrochloric, hydrobromic>nitric>*p*-toluene-sulfonic>picric>oxalic, acetic.

Use of Oxidants Other than Oxygen Gas. Ozone has been used to a limited extent in alkene oxidation. The ozone acts as an oxidant and also as a catalyst for the alkene-oxygen reaction. Mixtures of ethene and oxygen normally become explosive at temperatures³⁶² above 500°, but, in the presence of ozone, explosive reactions occurred around 400°.

Cis-glycols, which have not been widely investigated, are formed by the reaction of alkenes and hydrogen peroxide in the presence of catalysts.³⁶³ Inasmuch as hydrogen peroxide without a catalyst has no effect on an alkene double linkage, catalytic action may consist of splitting of hydrogen peroxide into hydroxyl radicals which then add to the double bond.³⁶⁴ Osmium tetroxide is a suitable catalyst.³⁶⁵ Hydrogen peroxide with vanadium pentoxide or chromium trioxide produced the glycol from 2-methyl-2-butene. A pentene-hydrogen peroxide reaction over ferrous sulfate yielded acetone, acetaldehyde, formic acid, and carbon dioxide, but no glycols were detected.³⁶⁶

Selenium dioxide and ethene reacted slightly at room temperature to produce the trimeric glyoxal.³⁴¹ The propene reaction was similar to that of ethene, but higher alkenes reacted only at elevated temperatures and produced mixtures too complex for analysis.

Oxidation of alkenes with dilute potassium permanganate results in the addition of two hydroxyl groups at the point of unsaturation. Prolonged oxidation or use of more concentrated acid causes complete oxidation to carbon dioxide and water. When higher alkenes are oxidized with potassium permanganate, scission occurs at the double bond, producing two acids. This reaction is used as a test for the point of unsaturation of alkenes.

Oxidation of Alkynes

Very little work has been done on the oxidation of alkynes, and practically none on the homologs above ethyne. The ethyne-oxygen reaction gives glyoxal, formaldehyde, formic acid, hydrogen, and the monoxide and dioxide of carbon,^{321, 367} and is apparently chain-propa-

³⁶⁰ Lucas and Eberz, *J. Am. Chem. Soc.*, **56**, 460 (1934).

³⁶¹ Lucas and Liu, *ibid.*, **56**, 2138 (1934).

³⁶² Spence and Taylor, *ibid.*, **52**, 2399 (1930).

³⁶³ Milas and Sussman, *ibid.*, **59**, 2345 (1937).

³⁶⁴ Milas, *ibid.*, **59**, 2342 (1937).

³⁶⁵ Milas and Sussman, *ibid.*, **58**, 1302 (1936).

³⁶⁶ Barkhash, *J. Gen. Chem. (U.S.S.R.)*, **5**, 254 (1935) [*C. A.*, **29**, 5067 (1935)].

³⁶⁷ Spence and Kistiakowsky, *J. Am. Chem. Soc.*, **52**, 4837 (1930).

gated³⁶⁸ since an induction period³⁶⁹ and inhibition by an excess of oxygen were noted.³⁶⁷ At high pressures, increased surface-volume ratio lowered the reaction rate; at low pressures, similar surface changes had a slight accelerating influence.³⁷⁰ Nitrogen dilution³⁶⁷ of the ethyne-oxygen mixture had a slight retarding effect. Glyoxal and formaldehyde cannot be important chain carriers since the former had little influence on ethyne oxidation and the latter had an inhibitory effect.³⁷⁰

Ethyne has been oxidized in the presence of nitrogen oxides and a few metals. Nitrogen peroxide appreciably lowered the reaction temperature of ethyne and oxygen,³⁷¹ and the principal product was glyoxal.³⁷² Copper, silver, gold, nickel, iron, and platinum were also used as catalysts for the complete oxidation of ethyne.³⁷³

Potassium permanganate was used to oxidize ethyne, 2-pentyne, and 3,3-dimethyl-1-butyne to acids.³⁷⁴ In these reactions it is probable that any primary addition product immediately splits at the point of unsaturation. Selenium dioxide was used to oxidize 1-heptyne and 1-octyne.³⁷⁵ The initial reaction was the substitution of a hydroxyl radical on the carbon atom adjacent to the unsaturated carbon. Ethyne and oxygen saturated with water vapor and illuminated by a mercury arc produced oxalic acid and an aldehyde.³⁷⁶

The theories of peroxidation, hydroxylation, and bond activation, which were offered for the more saturated hydrocarbons,³⁷⁷ may also be applied to the alkynes.^{377, 378}

Low-temperature oxidations have been carried out on mixtures of aliphatic hydrocarbons such as gasolines and lubricating oils, and this reaction is responsible for gum formation. Since there has been little attempt to carry out these reactions on pure hydrocarbons, these are omitted from this study.

³⁶⁸ Kistiakowsky and Lenher, *ibid.*, **52**, 3785 (1930).

³⁶⁹ Spence, *J. Chem. Soc.*, 686 (1932).

³⁷⁰ Steacie and McDonald, *J. Chem. Phys.*, **4**, 75 (1936).

³⁷¹ Lenher, *J. Am. Chem. Soc.*, **53**, 2962 (1931).

³⁷² Lenher, *ibid.*, **53**, 3737 (1931).

³⁷³ Davies, *Phil. Mag.*, **23**, 409 (1937).

³⁷⁴ Krestinsky and Kelborskaja, *Ber.*, **68**, 512 (1935).

³⁷⁵ Guillemonat, *Compt. rend.*, **201**, 904 (1935).

³⁷⁶ Livingston, *J. Am. Chem. Soc.*, **53**, 3909 (1931).

³⁷⁷ Bone, *Proc. Roy. Soc. (London)*, **162A**, 502 (1937).

³⁷⁸ Bodenstein, *Z. physik. Chem.*, **12B**, 151 (1931).

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CHAPTER 2

ALICYCLIC COMPOUNDS AND THE THEORY OF STRAIN

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INTRODUCTION

Carbocyclic compounds are classified on the basis of their behavior as aromatic or alicyclic.* With the exception of cyclopropane (generally regarded as the first member of the cycloalkane series) and its derivatives, the alicyclic compounds possess chemical properties very similar to those of the aliphatic series. It follows that in most instances our knowledge of aliphatic compounds can be transferred to the members of the alicyclic group. On this account, the chemistry of alicyclic compounds is of interest primarily because of stereochemical properties inherent in the ring form as opposed to open-chain structures. The chemical manifestations of space factors in this field are most pronounced in connection with reactions which involve the opening and closing of rings, and in the alteration of properties of functional groups which are a part of the ring or are directly attached to it.




Cyclohexane and its derivatives can be made by the addition of hydrogen to the corresponding aromatic compounds, and, for this reason, they have been called *hydroaromatic* compounds. It is possible to prepare aromatic compounds also by dehydrogenation of the corresponding cyclohexane derivatives. However, this relationship of the cyclohexane group to the aromatic series is almost entirely a genetic one; the two classes differ radically in their chemical properties.

This close connection between aromatic and alicyclic compounds is undoubtedly responsible for the fact that, of the latter group, the six-membered type was the first to be prepared. Indeed, until about 1880 it was generally supposed that rings smaller or larger than this could not exist.¹ All attempts to synthesize such rings had been fruitless, and they had not been found in nature. Moreover, there were theoretical grounds for this opinion, for it was evident that the smaller rings, at least, could not be made from carbon atoms having the rigid tetrahedral form which had been used so successfully in solving other structural problems. If the four bonds of a carbon atom are directed toward the vertices of a regular tetrahedron each forms an angle of $109^{\circ} 28'$ with the others. As a matter of fact, it is impossible, by use of such atoms, to

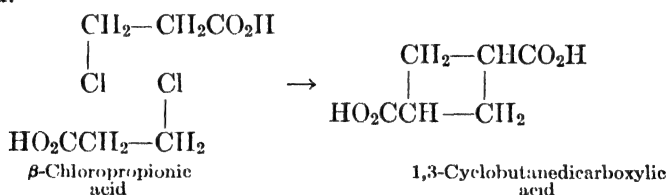
* The term alicyclic was suggested by Bamberger, *Ber.*, **22**, 769 (1889).

¹ Meyer, *Ann.*, **180**, 192 (1876).

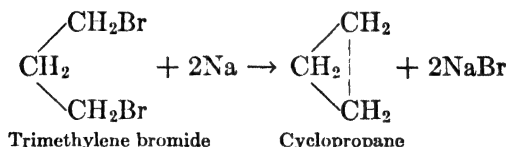
construct any ring of fewer than five members. The following table shows the angles which are required for the formation of the smaller rings, together with the deviation in each case of the valence bond from the normal position in the regular tetrahedron.

| Hydrocarbon | Formula | Angle | Deviation |
|------------------------------|--|-----------|----------------|
| Ethylene (cycloethane) | $\text{CH}_2=\text{CH}_2$ | 0° | $54^\circ 44'$ |
| Cyclopropane..... | CH_2-CH_2  | 60 | $24^\circ 44'$ |
| Cyclobutane..... | CH_2-CH_2  | 90 | $9^\circ 44'$ |
| Cyclopentane..... | CH_2-CH_2  | 108 | $0^\circ 44'$ |

Between 1880 and 1885, however, came a rapid succession of events which revolutionized chemists' ideas of ring compounds and laid the foundations of modern alicyclic chemistry. The first of these was the discovery of Markownikoff and Krestownikoff that β -chloropropionic acid, when heated with dry sodium ethoxide, was converted into a compound containing a ring of four carbon atoms—1,3-cyclobutanedicarboxylic acid.²



Almost immediately after this Freund³ succeeded in making cyclopropane—a hydrocarbon containing a three-membered ring—by the action of sodium on trimethylene bromide.

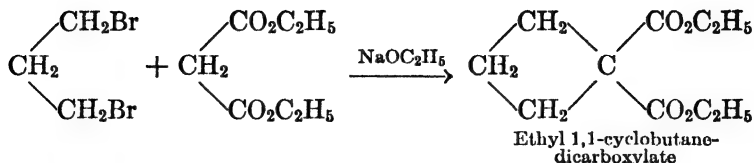


A little later Perkin⁴ found that ethyl malonate condenses with trimethylene bromide in the presence of sodium ethoxide to give ethyl 1,1-cyclobutanedicarboxylate.

² Markownikoff and Krestownikoff, *Ann.*, **208**, 333 (1881).

³ Freund, *Monatsh.*, **3**, 626 (1882).

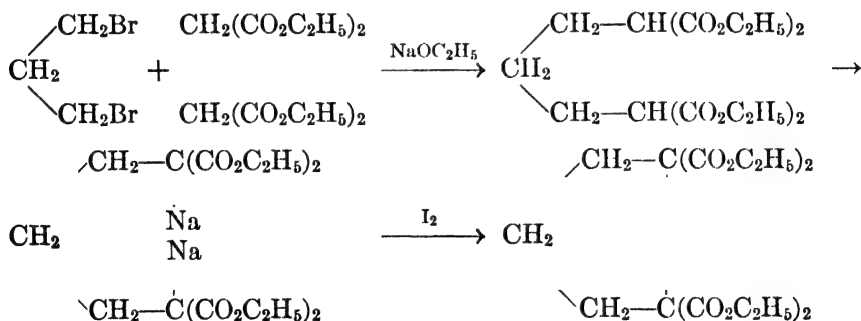
⁴ Perkin, *Ber.*, **16**, 1793 (1883).



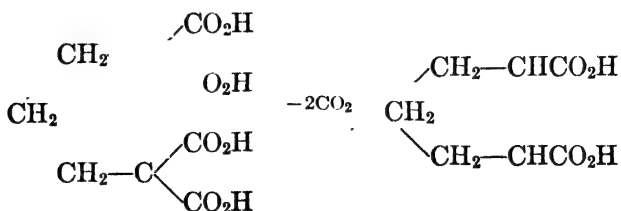
These results established the existence of three- and four-membered carbon rings and demanded drastic revision of the current opinions regarding the stereochemical character of the carbon atom.

Baeyer's Strain Theory. An ingenious and very plausible solution to the problem was advanced by Baeyer,⁵ who assumed that the normal angle between the valence bonds of carbon was $109^\circ 28'$, but *that it was possible for this angle to be altered*. Any deviation from this angle, however, was supposed to bring about a condition of *strain* which, according to the theory, was attended by a corresponding decrease in stability. The greater the strain involved, the less would be the stability of the resulting compound.

Striking confirmation of this theory was obtained almost at once by Perkin,⁶ who succeeded in preparing a compound containing the *cyclopentane* ring. By condensation of two molecules of malonic ester with one of trimethylene bromide, he obtained a tetracarboethoxypentane whose sodium derivative, when treated with iodine, gave ethyl 1,1,2,2-cyclopentanetetracarboxylate.



Hydrolysis of the ester gave an acid which, when heated, lost carbon dioxide and yielded 1,2-cyclopentanedicarboxylic acid.



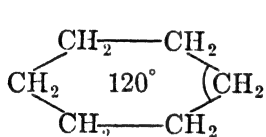
⁵ Baeyer, *Ber.*, **18**, 2277 (1885).

⁶ Perkin, *Ber.*, **18**, 3246 (1885).

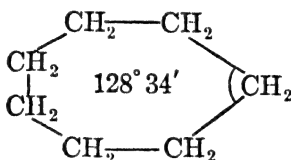
It should be pointed out that, according to Baeyer's theory, the cyclopropane ring, since it possessed greater strain, should be less stable than the cyclobutane ring, and that, in turn, the latter should be less stable than the cyclopentane ring. The 1,2-cyclopentanedicarboxylic acid was, indeed, found to be extremely stable, and so completely fulfilled the predictions of the theory.

It may be said at once that, for hydrocarbons having rings smaller than that of cyclohexane, the theory of Baeyer is in fairly satisfactory agreement with the facts which are known at the present time, although the physical nature of the strain is not yet fully understood.

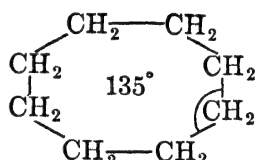
Strainless Rings. An integral part of Baeyer's strain theory was that the carbon atoms of the ring must lie in a plane, and, on this basis, he predicted that the formation of large rings would involve *negative* strain. From an inspection of the following figures, it is evident that, in cyclohexane and compounds containing large rings, the planar configuration required that the angle formed by the valence bonds be somewhat greater than normal, and that the amount of this stretching is greater in proportion to the size of the ring.



Cyclohexane



Cycloheptane



Cyclooctane

This postulate was supposed to account for the fact that rings of more than six members had not been made or discovered in nature, and were presumably very unstable. Moreover, it implied that very large rings would be incapable of existence.

This part of Baeyer's theory has proved to be misleading if not entirely erroneous. Sachse⁷ was the first to perceive that the so-called negative strain need not exist and that the large rings might, in fact, be strainless. This idea was disregarded by chemists for nearly thirty years, but was eventually revived and elaborated by Mohr,⁸ and within recent years has been almost fully confirmed by experiment. The idea of Sachse may be illustrated by reference to models. When, by the use of tetrahedral atoms, models are constructed for rings containing more than five members it is found that the atoms forming the ring do not lie

⁷ Sachse, *Ber.*, **23**, 1363 (1890); *Z. physik. Chem.*, **10**, 203 (1892).

⁸ Mohr, *J. prakt. Chem.*, [2] **98**, 349 (1918); **103**, 316 (1922).

in a plane as they do with smaller rings. For example, six tetrahedral atoms may be united as shown in Fig. 1 or 3.

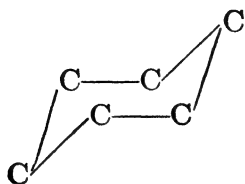


FIG. 1

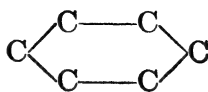


FIG. 2

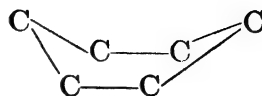


FIG. 3

These models differ from the planar one shown in Fig. 2 in that they can be constructed without distortion of the tetrahedral form of the atoms involved. For the atoms to be in a plane as in Fig. 2 it is necessary, as noted earlier, to introduce "negative" strain; i.e., increase the angle between the annular bonds to values greater than the normal.

Since stable rings which contain more than thirty members are now known there is no necessity for assuming a planar form for any ring of more than five members. As will appear in the sequel, this theory has been confirmed by the work of Ruzicka, Hückel, Ziegler, and others. Rings of this type are known as *strainless rings*. The compounds containing very large carbon rings have been made in a variety of ways and have been found to possess stabilities comparable with those of the corresponding open-chain compounds. It should be mentioned, however, that there is evidence that some strain persists even in the compounds containing very large rings.⁹

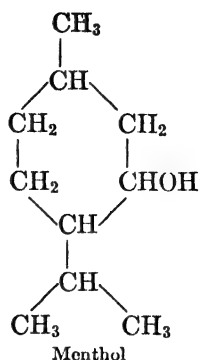
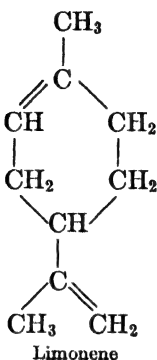
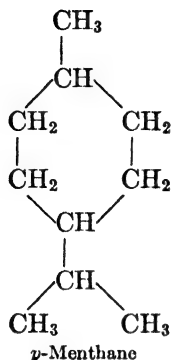
The Occurrence of Alicyclic Compounds in Nature. Rings of the alicyclic type abound in natural products. Most of these consist of five or six members. Thus the nonbenzenoid cyclic hydrocarbons obtained from petroleum—generally known as *naphthenes*—as well as naphthenic acids¹⁰ are chiefly derivatives of cyclopentane and cyclohexane.

The most important group of naturally occurring alicyclic compounds is formed by the *terpenes* and their derivatives. These occur in essential oils, particularly those from citrus fruits; they are also found in oil of turpentine and similar materials made from coniferous trees. They embody rings of all sizes up to and including the cyclohexane ring, which is the one most frequently encountered. A glimpse of this vast field is afforded by a list of the skeletal structures of the principal types.

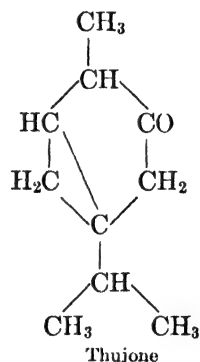
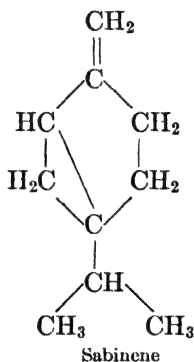
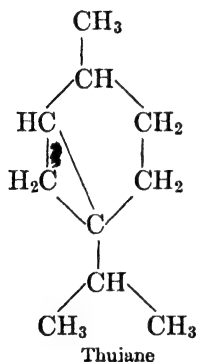
The most important monocyclic compounds in this group are derivatives of *p*-menthane. Limonene and menthol are examples:

⁹ Carothers and Hill, *J. Am. Chem. Soc.*, **55**, 5043 (1933).

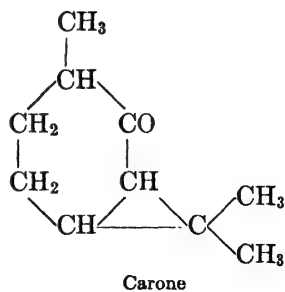
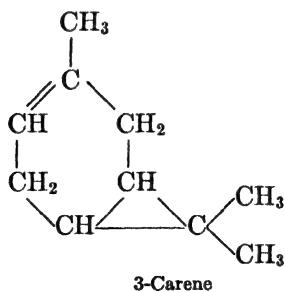
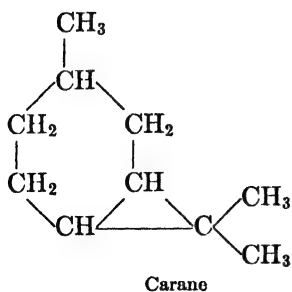
¹⁰ v. Braun, *et al.*, *Ann.*, **490**, 100 (1931).



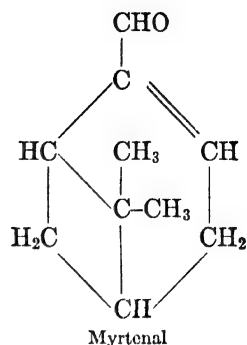
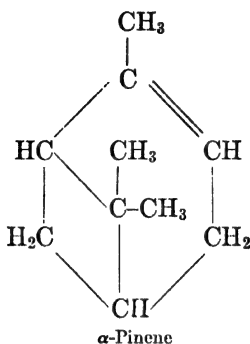
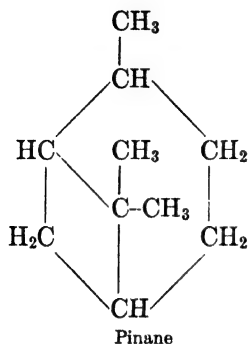
The bicyclic compounds which have the cyclopropane ring are derivatives of thujane and carane. Sabinene and thujone are among the thujane derivatives which occur naturally.



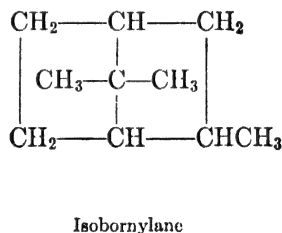
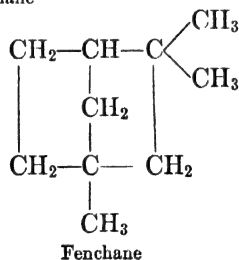
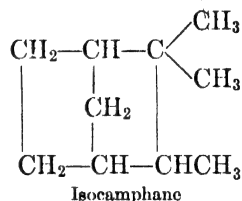
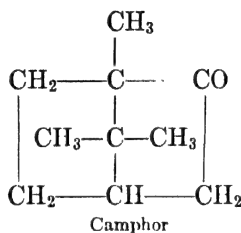
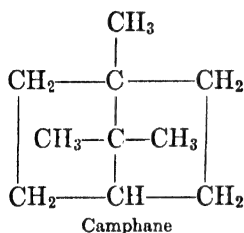
The carane group includes 3-carene and carone.



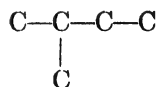
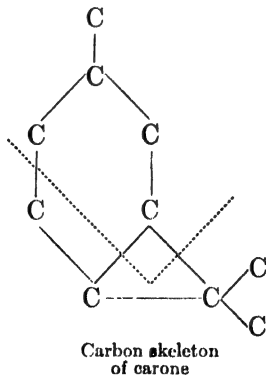
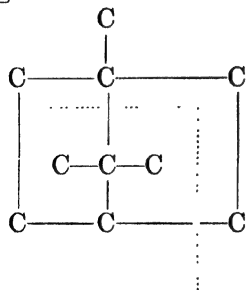
The pinane derivatives, such as α -pinene and myrtenal, contain a four-membered ring in addition to the usual six-membered ring.



Camphor belongs to the camphane series, the members of which have a structure made up of two condensed five-membered rings. The isocamphane, fenchane, and isobornylane groups are similarly constituted.



An inspection of the foregoing structures reveals the striking fact that each is made up of two isoprene units, as is shown by the following diagram:



The structural unit represented by isoprene is also to be found in open-chain terpenes and sesquiterpenes.

Complex alicyclic ring systems also appear in many of the more complicated structures which have been found in nature. Among these are the higher terpene compounds, the sex hormones, the sterols, the bile acids, the resin acids, the sapogenins, and certain alkaloids.

The elucidation of the structures of such natural products and the synthesis of their analogs has always been one of the most attractive and useful occupations of organic chemists, and, from the preceding section, it is evident that much of the work in this field has been concerned with the synthesis of alicyclic rings. Fortunately, the six-membered ring, which is by far the one most frequently encountered, can be made by hydrogenation of the benzene ring. For the preparation of rings of other sizes the chemist has used three types of methods, namely, ring closures, ring expansions, and ring contractions.

THE SYNTHESIS OF ALICYCLIC COMPOUNDS FROM AROMATIC COMPOUNDS

The transformation of benzenoid compounds into the corresponding cyclohexane derivatives by hydrogenation is a very general method which is frequently used. The preparation of cyclohexane by hydrogenation of benzene over nickel at 180–200° was first accomplished by Sabatier and Senderens.¹¹ Naphthalene, under similar conditions, yields tetrahydronaphthalene (tetralin), and at higher temperatures and pressures decahydronaphthalene (decalin) is produced.

The partially hydrogenated rings are very reactive, and in the presence of hydrogen acceptors tend to revert to the benzenoid condition by loss of hydrogen. In fact, disproportionation is frequently observed. Thus, Zelinsky and Pavlov^{12, 13} showed that, in the presence of palladium or platinum, and at temperatures somewhat above their boiling points, both cyclohexene and cyclohexadiene are irreversibly converted into mixtures of benzene and cyclohexane.

Some aromatic compounds, such as benzoic and phthalic acids, can be reduced by means of sodium and alcohol, but the method does not always give good yields.

Various types of catalysts have been used in the hydrogenation (p. 817) of benzene. Sabatier and Senderens discovered that nickel was a catalyst for the hydrogenation of various aromatic compounds in the

¹¹ Sabatier and Senderens, *Compt. rend.*, **132**, 210 (1901).

¹² Zelinsky, *Ber.*, **58B**, 864 (1925).

¹³ Zelinsky and Pavlov, *Ber.*, **66B**, 1420 (1933).

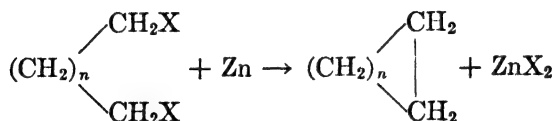
vapor phase. This method has not been particularly useful in the laboratory. The method of Ipatieff for hydrogenation of compounds in the liquid phase at high pressures has led to the development of the present practice which involves improved nickel catalysts and pressures from 50 to 200 atmospheres at temperatures from 100 to 200°. By this method it is possible to hydrogenate almost any aromatic compound. For reduction at ordinary temperatures and pressures platinum black (Willstätter), colloidal platinum (Skita), and platinum oxide-platinum black (Adams)¹⁴ have been used.

THE SYNTHESIS OF ALICYCLIC COMPOUNDS BY MEANS OF RING CLOSURES

Almost every type of reaction involving the formation of a carbon-carbon bond has been used successfully in the synthesis of alicyclic compounds from open-chain compounds. The probability that a given type of intermolecular condensation reaction can be made to take place intramolecularly depends largely upon the size of the ring which would result. Other factors, however, such as the number and kind of substituents present, are often of great importance. The old view, that the ease of ring closure was a measure of the strain of the resulting ring system, has now been generally abandoned. It has become evident that steric factors other than ring tension play an important part in determining the tendency of a given ring closure to take place.

Of the numerous methods of ring closure to be found in the literature, the following are among those which have proved to be most useful and most interesting from a theoretical point of view.

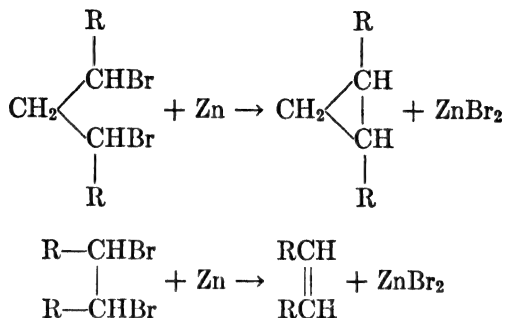
The Freund Reaction. The coupling together of two alkyl residues by the action of metals such as sodium or zinc on halogen compounds has been widely used; yields of 50 per cent or better are obtained in many instances. A similar condensation occurs when polymethylene halides react with a metal.



This method has been used to prepare rings of three, four, five, and six members, but gives good yields only in the cyclopropane series. Cyclobutane itself and cycloheptane have not been prepared in this way. The synthesis of cyclopropane and its homologs is usually carried out by treatment of the bromide with zinc in alcohol; the yields are sometimes

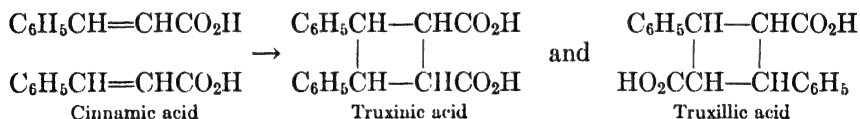
¹⁴ Adams and Marshall, *J. Am. Chem. Soc.*, **50**, 1970 (1928).

as high as 68 per cent of the theoretical amount.¹⁵ A method has been developed for making the hydrocarbon by the interaction of 1,3-dichloropropane and zinc in the presence of sodium iodide.¹⁶ This type of reaction illustrates the close similarity of the chemistry of the cyclopropanes to that of the olefins (cycloethanes).

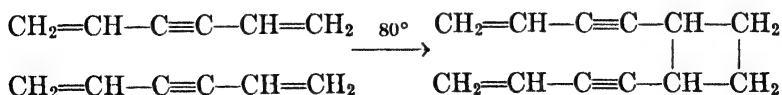


From the standpoint of the strain theory, it is interesting to note that the formation of the olefin takes place more easily than that of the three-membered ring which, in turn, forms more readily than the cyclobutane ring—a result which is exactly opposite to that predicted by the original theory of Baeyer.

Condensations of Unsaturated Compounds. The tendency of olefinic and acetylenic compounds to polymerize frequently leads to the formation of alicyclic rings. Thus, cinnamic acid under the influence of sunlight is slowly transformed into truxillic and truxinic acids.



Self-addition of this type does not occur with the simplest olefins, but is frequently realized with those of higher molecular weight. Such processes can generally be reversed by heating. It has been shown that divinylacetylene undergoes this type of reaction.¹⁷



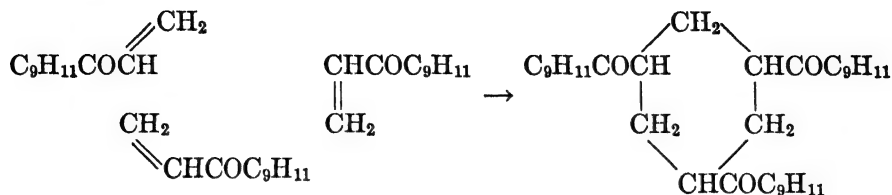
Cyclization of an olefinic compound to a cyclohexane derivative has also been observed. When heated in the presence of methanol and

¹⁵ Lespieau and Wakeman, *Bull. soc. chim.*, **51**, 384 (1932).

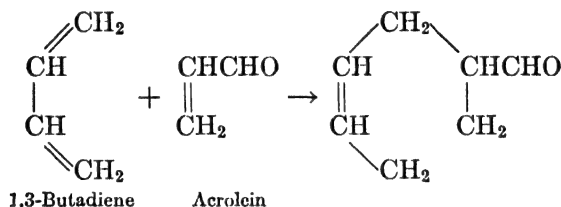
¹⁶ Hass, McBee, Hinds, and Gluesenkamp, *Ind. Eng. Chem.*, **28**, 1178 (1936).

¹⁷ Cupery and Carothers, *J. Am. Chem. Soc.*, **56**, 1167 (1934).

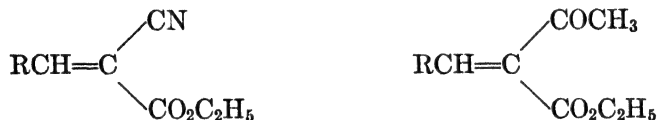
potassium carbonate, vinyl mesityl ketone trimerizes to 1,3,5-trimesitylcyclohexane.¹⁸



The Diene Synthesis. 1,3-Butadiene and similarly constituted dienes have been found to condense with a variety of unsaturated aldehydes, ketones, esters, quinones, and the like to give six-membered rings.¹⁹ The reaction was discovered by Diels and Alder²⁰ and is generally referred to as the Diels-Alder or diene synthesis. It may be illustrated by 1,3-butadiene and acrolein which combine to give a tetrahydrobenzaldehyde.



In place of the acrolein it is possible to use quinone, malic anhydride, and a large number of other α,β -unsaturated carbonyl compounds. Derivatives of cyanoacetic and acetoacetic esters of the following types may be included:



However, the synthesis is not restricted to α,β -unsaturated carbonyl compounds. It has been extended also to styrene, vinyl chloride, vinyl acetate, and allyl chloride.

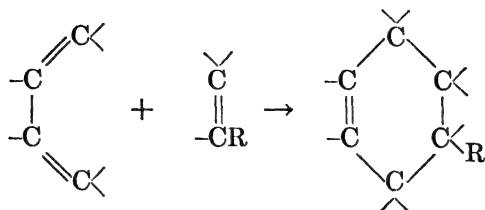
Isoprene, 2,3-dimethyl-1,3-butadiene, cyclopentadiene, furan, and numerous other substances containing the conjugated diene structure undergo this type of condensation. So general is the reaction, in fact, that it can be used as a test for the presence of a conjugated olefinic linkage in a molecule. The reaction invariably leads to the formation of

¹⁸ Fuson and McKeever, *ibid.*, **62**, 2088 (1940).

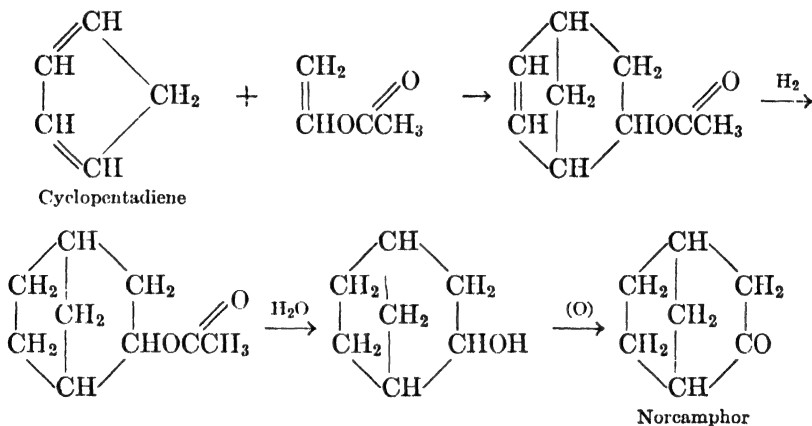
¹⁹ Diels and Alder, *Fortschr. Chem. Org. Naturstoffe*, **3**, 1 (1939).

²⁰ Diels and Alder, *Ann.*, **460**, 98 (1928).

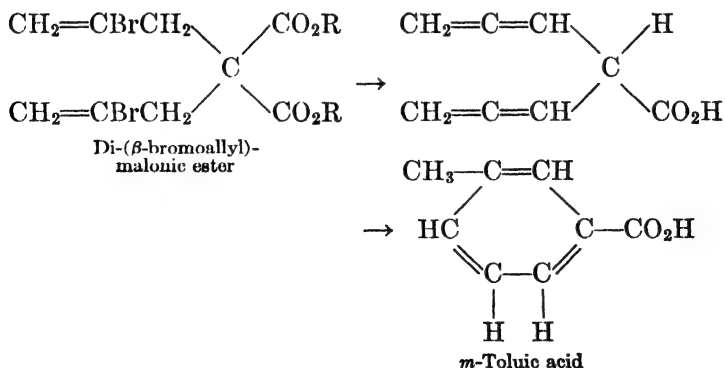
a six-membered ring. It may be represented by the following generalized equation.



If the diene forms part of a ring the product will be a bicyclic compound. An example is the condensation of vinyl acetate with cyclopentadiene; the product is the acetate of a bicyclic alcohol, which can be converted to norcamphor.²¹

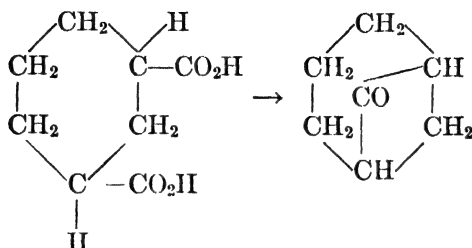


Intramolecular condensation may also lead to ring formation. A very interesting example of this is the transformation of di-(β -bromoallyl)-malonic ester into *m*-toluic acid. The condensation is effected by use of alcoholic potash and presumably involves the formation of a diallene as an intermediate.

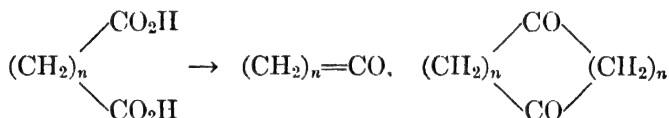


²¹ Alder and Rickert, *Ann.*, **543**, 1 (1940).

In conformity with this, no cyclization whatever is observed. A very special instance of the closure of the four-membered ring by this method has been reported by Stark, who obtained "demethylated pinone" by heating the calcium salt of hexahydroisophthalic acid.²⁵



In place of the calcium salt, others, such as the barium, cerium, yttrium, and thorium compounds, have likewise been subjected to thermal decomposition. Ruzicka and Brugger have shown that the thorium salts often give much better yields than the calcium salts. Using this method, Ruzicka, Stoll, and Schinz have prepared cycloalkanones having very large rings.²⁶ Cycloalkanediones are also obtained.



The largest ring so far reported is a cycloalkanedione of thirty-four members. These compounds will be described in more detail in a subsequent section.

The mechanism of this reaction is inherently obscure. It is known, however, that the yields depend to some extent on the metal used. This is clearly set forth in the following table, which contrasts the yields obtained by the use of thorium salts with those afforded by the old method (using calcium salts).

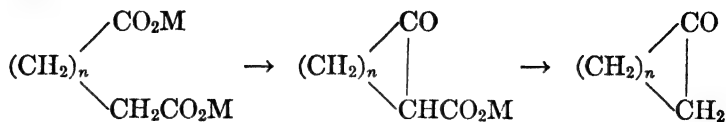
| ACID | PER CENT YIELD OF CYCLOALKANONE USING | |
|----------|--|--------------|
| | CALCIUM SALT | THORIUM SALT |
| Glutaric | 0 | 0 |
| Adipic | 45 | 15 |
| Pimelic | 40-50 | 70 |
| Suberic | 35 | 50 |
| Azelaic | 5 | 20 |

Recent work indicates that the ring closure resembles the Dieckmann

²⁵ Stark, *Ber.*, **45**, 2369 (1912).

²⁶ Ruzicka, Stoll, and Schinz, *Helv. Chim. Acta*, **9**, 249 (1926).

reaction, the salt of a keto acid being formed and subsequently decomposed to give the cyclanone.²⁷



In an attempt to formulate a rational explanation of the variation in yield with increase in the number of atoms in the ring Ruzicka and his co-workers²⁸ postulated that the cyclization depends on two factors. One, the distance between the ends of the chain, will obviously favor the formation of small rings and oppose that of large rings. The second factor, according to the theory, depends on the intrinsic stability of the rings, and will, in consequence, favor the formation of strainless rings. Expressed graphically this postulate pictures the actual yield (curve *c*) as the resultant of the "distance factor" (curve *a*) and the strain factor (curve *b*) as shown in the following figure:

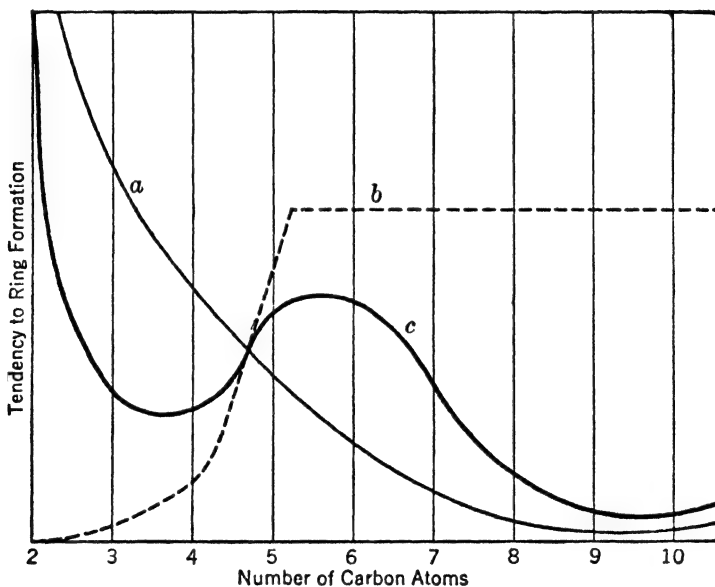


FIG. 4 *

An interesting and useful modification of the foregoing method was developed by Blanc, who found that slow distillation of the anhydrides of certain dibasic acids produced cycloalkanones.²⁹ Only a little cyclo-

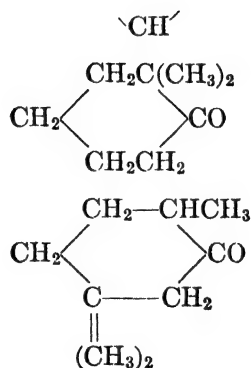
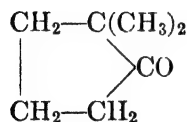
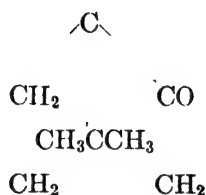
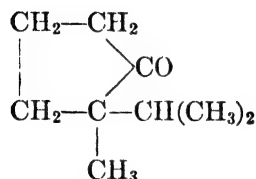
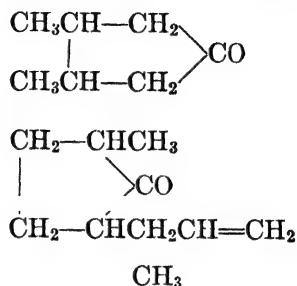
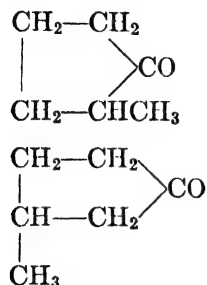
²⁷ Neunhoeffer and Paschke, *Ber.*, **72B**, 919 (1939).

²⁸ Ruzicka, Brugger, Pfeiffer, Schinz, and Stoll, *Ber.*, **9**, 499 (1926).

* From Ruzicka and co-workers, *Helv. Chim. Acta*, **9**, 499 (1926). (Courtesy of the publishers.)

²⁹ Blanc, *Compt. rend.*, **144**, 1356 (1907).

heptanone could be produced in this way, and even for cyclopentanone and cyclohexanone the yields did not exceed 50 per cent. Alkyl groups have a remarkable effect on the yields obtained as is shown by the following illustrative examples, in all of which the yields are nearly quantitative.



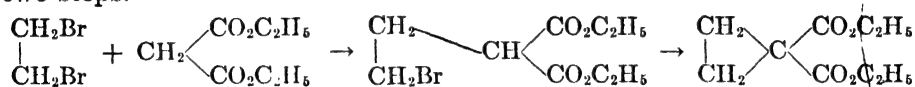
This is a striking example of the general rule that the presence of alkyl groups and particularly the *gem*-methyl groups ($(\text{CH}_3)_2\text{C}$) enhances the tendency of a chain to undergo cyclization. The original strain theory of Baeyer takes no account of the influences of substituents.

Blanc's results are summarized in what is known as *Blanc's rule*,²⁹ which states that when adipic and pimelic acids are heated with acetic anhydride and then distilled (at about 300°) cycloalkanones are formed, whereas succinic and glutaric acids under similar conditions yield cyclic anhydrides. Blanc's rule has been used frequently in determining the constitution of dibasic acids of the hydroaromatic series.³⁰ It is now

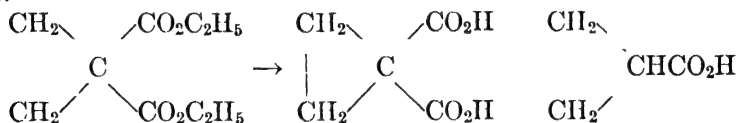
³⁰ Windaus, Hückel, and Revere, *Ber.*, **56**, 91 (1923).

known that this rule is not always valid; sometimes when the two carboxyl groups are attached to different rings, a seven-membered anhydride forms.³¹

Perkin's Method. The method of Perkin, already mentioned (p. 67), involves the use of compounds containing active methylene and methinyl groups together with polymethylene halides, and is capable of wide variation. Perhaps the simplest example is the preparation of cyclopropanecarboxylic acid from ethylene bromide and malonic ester. The condensation takes place in the presence of sodium ethoxide and involves two steps.*

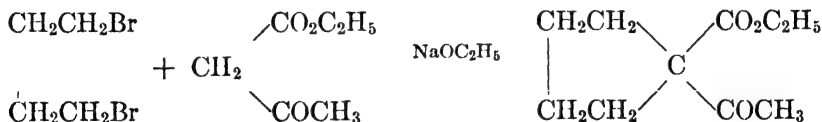


Saponification of the ester yields 1,1-cyclopropanedicarboxylic acid which when heated passes into the monobasic acid by loss of carbon dioxide.

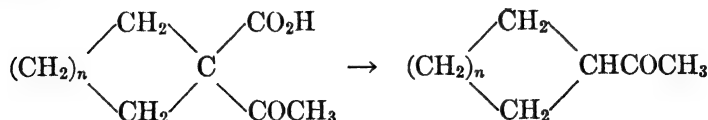


The method has been used similarly for the preparation of the corresponding four-, five-, six-, and seven-membered rings. The yields correspond approximately to the predictions based on the assumption that the tendency of a ring to form is governed by the amount of strain it possesses; i.e., they fall in the following order: $\text{C}_5 > \text{C}_6 > \text{C}_4 > \text{C}_3 > \text{C}_7$. In the case of the cyclopentane derivative the yield is nearly quantitative.

Similar results are obtained with acetoacetic ester. Thus, with tetramethylene bromide the principal product is ethyl 1-aceto-1-cyclopentancarboxylate.³²



Hydrolysis and decarboxylation in these cases lead to the formation of the corresponding cycloalkyl methyl ketones.

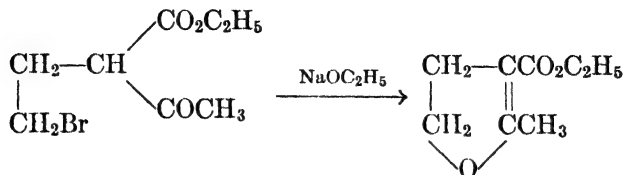


³¹ Windaus, *Z. physiol. Chem.*, **213**, 147 (1932).

* Meincke, Cox, and McElvain showed that use of the magnesium derivative of malonic ester led to the formation of a small amount of 1,1,4,4-tetracarboethoxycyclohexane. *J. Am. Chem. Soc.*, **57**, 1133 (1935).

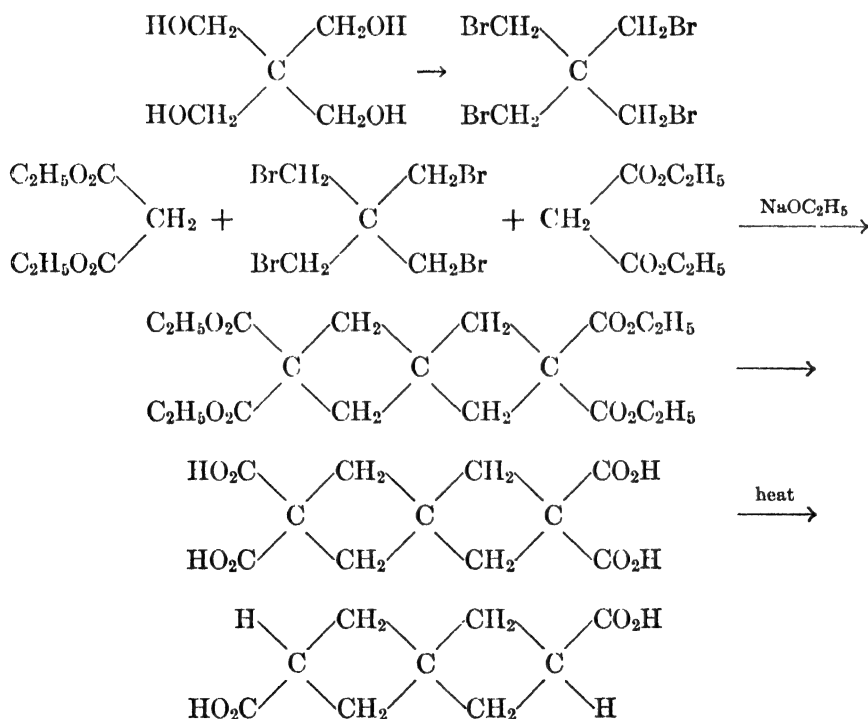
³² Goldsworthy, *J. Chem. Soc.*, 377 (1934).

This synthesis has been carried out for the cases in which $n = 0, 2, 3$, and 4, but not for that in which $n = 1$. In the condensation with ethylene bromide the second phase of the reaction gives a second product derived from the enol form of the ketone.



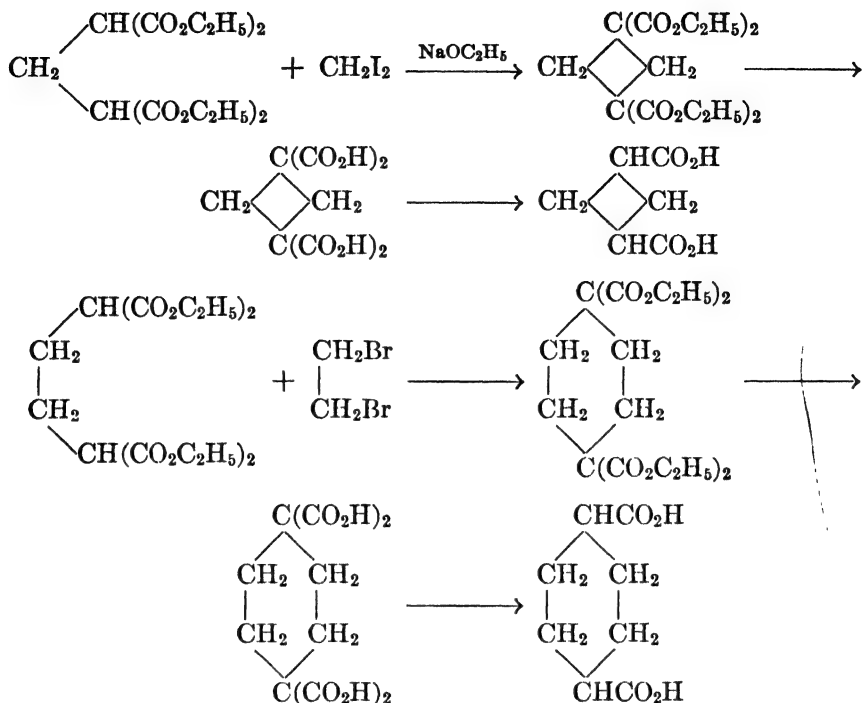
In the case of trimethylene bromide ($n = 1$) the cyclic ether—a derivative of dihydro-1,4-pyran—is the sole product.

Of particular interest is the resolvable (p. 340) spiroheptanedicarboxylic acid prepared from pentaerythritol by the following series of transformations: *

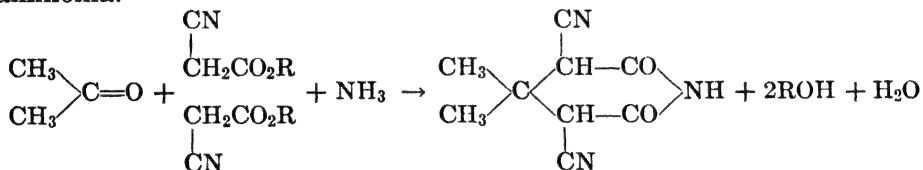


Methods were also devised by Perkin for the synthesis of cyclic acids in which the carboxyl groups were situated on different carbons. The following examples will suffice to show the broad scope of these methods.

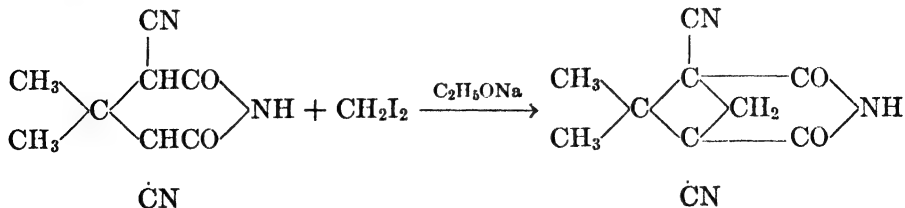
* The acid was prepared by Fecht [*Ber.*, **40**, 3883 (1907)] and resolved by Backer and Schurink [*Verslag. Akad. Wetenschappen Amsterdam*, **37**, 384 (1928)].



The synthesis of norpinic acid by Kerr³³ is a peculiar but very important example of this type of condensation. It involves the use of Guareschi's imide,³⁴ which is made from acetone, cyanoacetic ester, and ammonia.³⁵



In the presence of sodium ethoxide the imide condenses with methylene iodide in the following fashion:

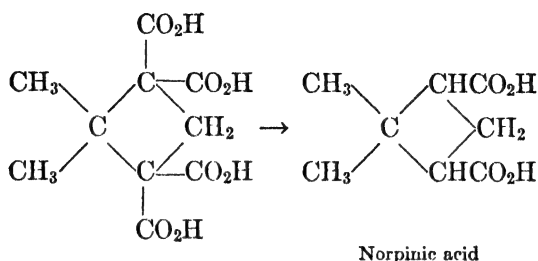


³³ Kerr, *J. Am. Chem. Soc.*, **51**, 614 (1929).

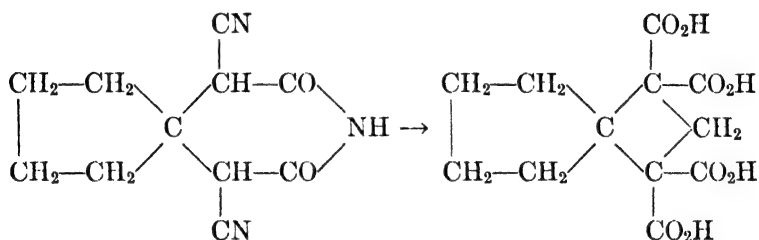
³⁴ Guareschi, *Atti. accad. sci. Torino*, **34**, 928 (1899).

³⁵ Kon and Thorpe, *J. Chem. Soc.*, **115**, 686 (1919).

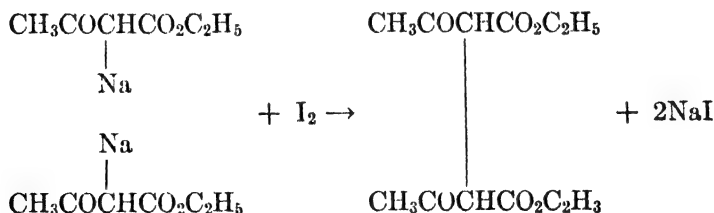
Saponification of this cyclobutane derivative yields a tetracarboxylic acid which when heated gives norpinic acid.



If a cycloalkanone is used in place of acetone this method leads to the formation of spirocycloalkane polybasic acids. Cyclopentanone will serve as an illustration.³⁶

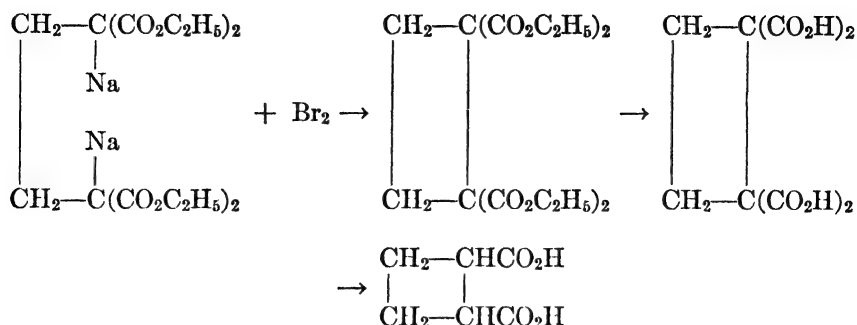


Another method of ring closure developed by Perkin has already been mentioned (p. 68); it depends on the fact that compounds containing active methylene or methinyl groups may be caused to undergo a coupling reaction of the type illustrated in the preparation of α,α' -diaceto-succinic ester from acetoacetic ester. To accomplish this result the sodium derivative of the latter is treated with bromine or iodine.

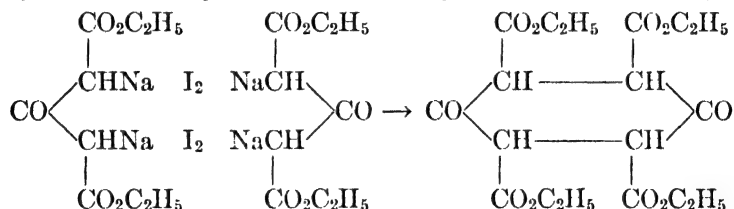


Applied to ethyl 1,1,4,4-butanetetracarboxylate, obtained from ethyl malonate and ethylene bromide or chloride, this method leads to the formation of the 1,2-cyclobutanedicarboxylic acid.

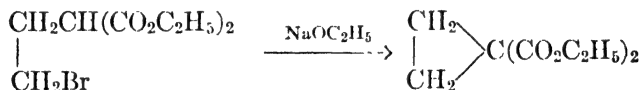
³⁶ Paul, *J. Indian Chem. Soc.*, **8**, 717 (1931).



This method can also be used to effect a dimolecular condensation. Thus, von Pechmann³⁷ prepared ethyl cyclohexane-1,4-dione-2,3,5,6-tetracarboxylate from ethyl acetonedicarboxylate in the following manner:

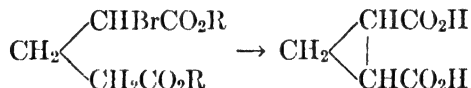


Cyclization by the Elimination of Hydrogen Halides. A molecule which contains an active hydrogen atom and a halogen atom suitably situated with respect to it can frequently be caused to form a ring by loss of a molecule of hydrogen halide. The second step of Perkin's original method is an example of this:



Markownikoff and Krestownikoff's early synthesis of 1,3-cyclobutanedicarboxylic acid (p. 67) apparently belongs in the same category.

Similar to this is Perkin's synthesis of 1,2-cyclopropanedicarboxylic acid from α -bromoglutaric ester by treatment with potassium hydroxide.



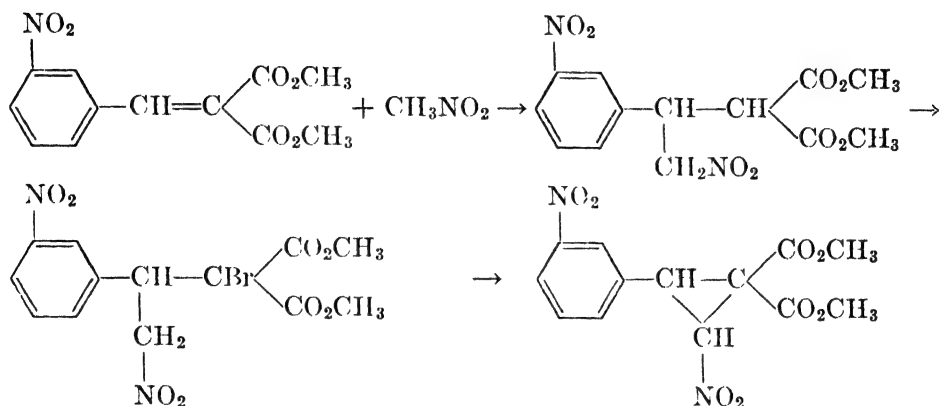
This method has been employed in the preparation of a wide variety of derivatives of cyclopropane.

A remarkable example of this type of cyclization is the conversion of neopentyl and neohexyl chlorides to 1,1-dimethylcyclopropane and 1,1,2-trimethylcyclopropane, respectively, under the influence of sodium:^{37a}

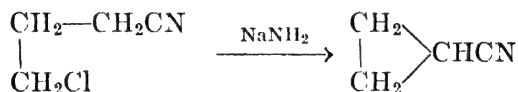
³⁷ v. Pechmann and Wolmann, *Ber.*, **30**, 2569 (1897).

^{37a} Whitmore, Popin, Bernstein, and Wilkins, *J. Am. Chem. Soc.*, **62**, 124 (1941); Whitmore and Carney, *ibid.*, **63**, 2633 (1941).

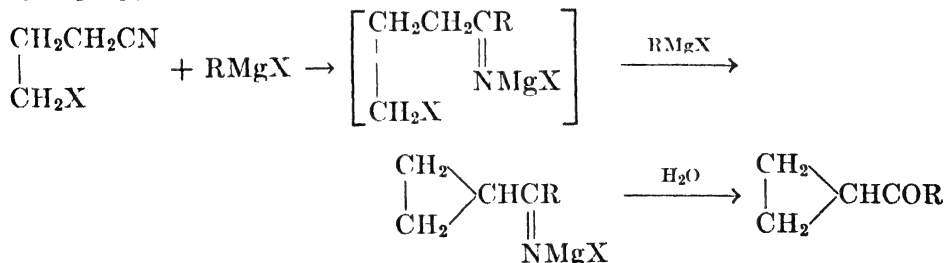
The Michael condensation (p. 682) leads to many types of molecules which may serve for the synthesis of cyclopropane derivatives. For such compounds Kohler has developed a method of cyclization which involves the removal of a molecule of hydrogen bromide by treatment of the bromine derivative with potassium acetate in methyl alcohol. The following example involving the use of nitromethane and methyl *m*-nitrobenzalmalonate will serve to indicate the wide applicability of this method:³⁸



A similar method of closing the cyclopropane ring is due to Henry, who found that γ -halonitriles, when treated with potassium hydroxide, gave the nitriles of the corresponding cyclopropanecarboxylic acids. By use of sodamide in liquid ammonia, γ -chlorobutyronitrile has been converted to the nitrile of cyclopropanecarboxylic acid in yields of 75–90 per cent.³⁹



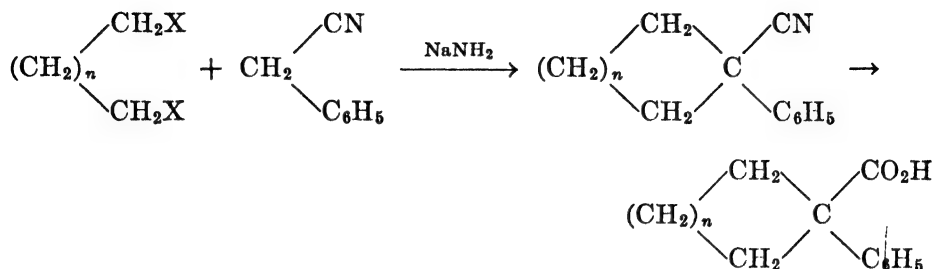
Bruylants' modification of this method involves the addition of a Grignard reagent (p. 504) to a γ -halonitrile and leads to the formation of cyclopropyl ketones.



³⁸ Kohler and Darling, *J. Am. Chem. Soc.*, **52**, 424, 1174 (1930).

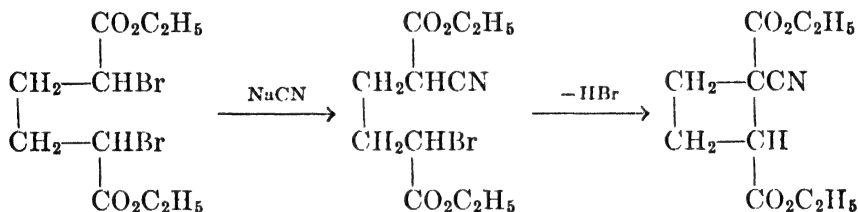
³⁹ Cloke, Anderson, Lachmann, and Smith, *ibid.*, **53**, 2791 (1931).

The condensation of phenylacetonitrile with polymethylene halides in the presence of sodamide furnishes a very useful method for the preparation of 1-phenyl-1-cycloalkanecarboxylic acids.



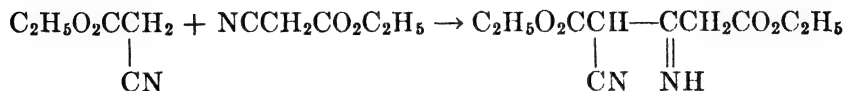
This method has been used for three-, four-, five-, and six-membered rings.⁴⁰

A superior method of synthesis of the cyclobutane ring involves the action of sodium cyanide on α, α' -dibromoadipic esters.⁴¹ Apparently the δ -bromonitrile is an intermediate product and the cyclobutane derivative is formed from it by loss of hydrogen bromide.



Hydrolysis and decarboxylation of the cyanoester lead to the formation of 1,2-cyclobutanedicarboxylic acid. Rydon's synthesis of norcaryophyllenic acid⁴² is based on this method.

Thorpe's Reaction. Nitriles having an active hydrogen atom may undergo dimerization in the presence of sodium ethoxide. Thus, under these conditions cyanoacetic ester combines with itself in the following fashion:



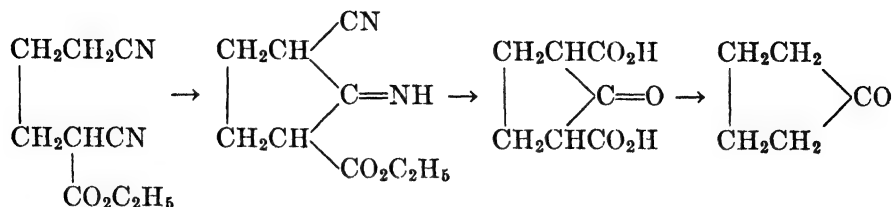
Applied to appropriate dinitriles this method leads to the formation of

⁴⁰ Case, *ibid.*, **55**, 2927 (1933); **56**, 715 (1934).

⁴¹ Fuson and Kao, *ibid.*, **51**, 1536 (1929).

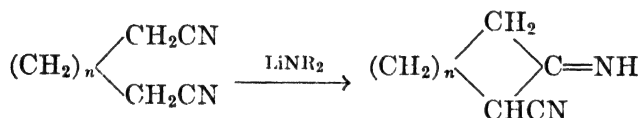
⁴² Rydon, *Chemistry & Industry*, **54**, 315 (1935).

cycloalkanone derivatives. Ethyl α,δ -dicyanovaleate, for example, may be converted into α,α' -cyclopentanonedicarboxylic acid.



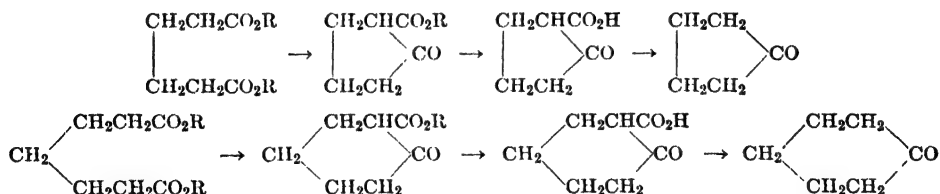
This acid loses carbon dioxide to give cyclopentanone.

This reaction has been used by Ziegler, Eberle, and Ohlinger⁴³ with brilliant success in the synthesis of very large rings. By the use of lithium amides it has been possible to obtain rings having more than thirty members. The remarkable feature of this discovery is that it affords yields of as high as 85 per cent of the theoretical amount. At the present time this is by far the best procedure available for synthesizing large carbon rings.



It is essential that these reactions be carried out at high dilution; this condition, it will be seen, favors the desired intramolecular condensation as opposed to the intermolecular combination.

Dieckmann's Acetoacetic Ester Method. The action of sodium on the esters of adipic and pimelic acids leads to the formation of five- and six-membered rings, respectively.

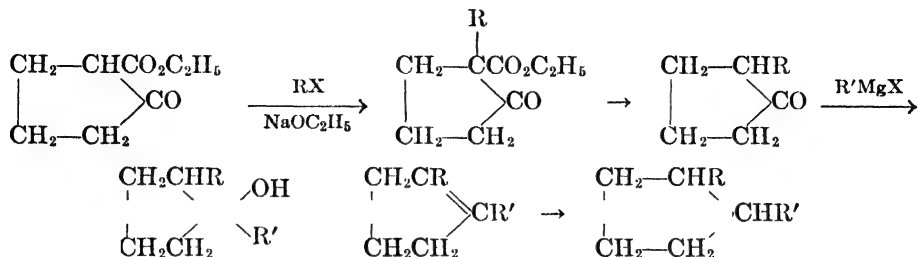


Since the initial condensation product is a β -keto ester it can be converted, by hydrolysis and loss of carbon dioxide, into the corresponding cycloalkanone; this conversion to the cycloalkanone serves to establish the structure of the keto ester. Also, it may be alkylated and in this way alkylcycloalkanones can be prepared. A general procedure for making 1,2-dialkylcycloalkanes depends on this method.⁴⁴ The second

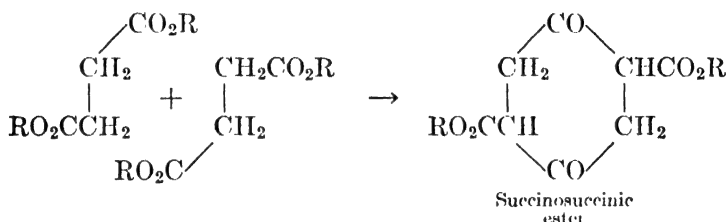
⁴³ Ziegler, Eberle, and Ohlinger, *Ann.*, **504**, 94 (1933).

⁴⁴ Chiurdoglu, *Bull. sci. acad. roy. Belg.*, **17**, 1404 (1932).

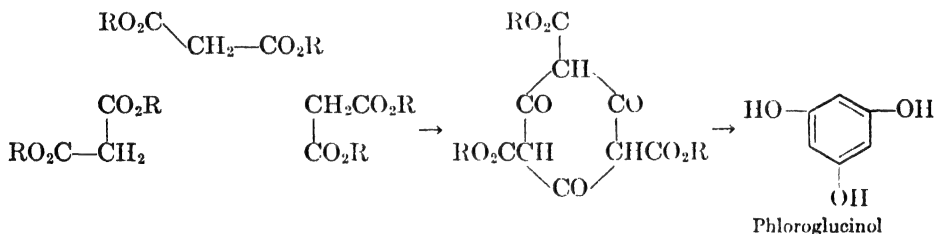
alkyl group is introduced by the use of the Grignard reagent; dehydration and then hydrogenation complete the synthesis.



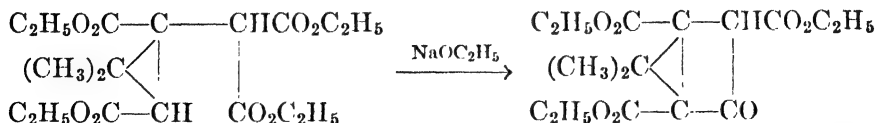
The acetoacetic ester method does not give three-membered rings. Succinic ester reacts with sodium to give succinosuccinic ester—a diketocyclohexane derivative.



Similarly, malonic ester is converted to a triketocyclohexane derivative; the structure of this product is established by the fact that the corresponding free acid loses carbon dioxide to give phloroglucinol.



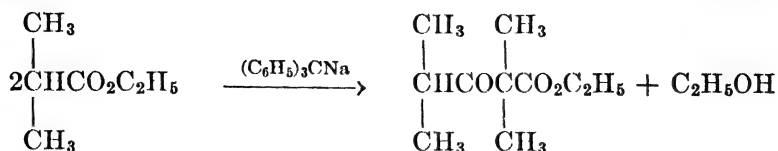
A very remarkable closure of a four-membered ring was effected by Perkin and Thorpe⁴⁵ by use of this method.



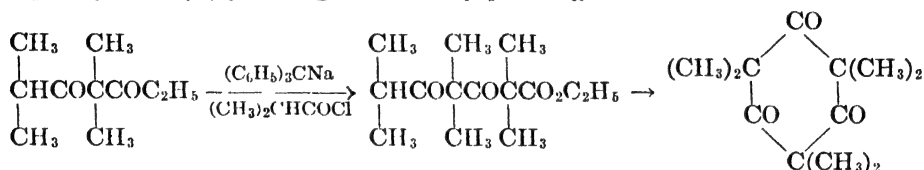
This reaction has attracted much attention, not only because of the unusual structure of the product, but also because it is one of the few known cases in which the acetoacetic ester condensation takes place on a carbon atom which holds only one hydrogen atom.

⁴⁵ Perkin and Thorpe, *J. Chem. Soc.*, **79**, 736 (1901).

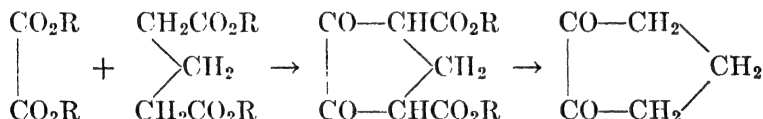
When sodium triphenylmethyl is used as the catalyst in place of sodium ethoxide, this type of reaction occurs readily. An example is the formation of ethyl isobutyrylisobutyrate from ethyl isobutyrate.



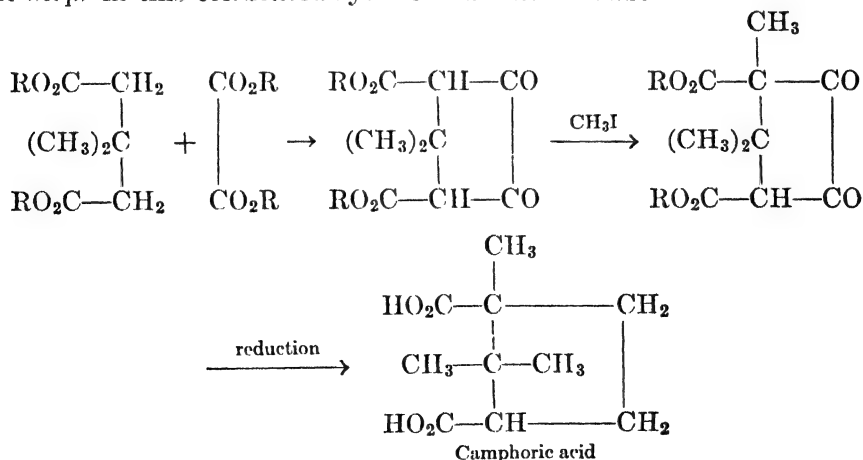
The keto ester forms an enolate with sodium triphenylmethyl which with isobutyryl chloride gives ethyl 2,2,4,4,6-pentamethyl-3,5-diketoheptanoate. The latter undergoes cyclization under the influence of sodium triphenylmethyl, yielding hexamethylphloroglucinol.⁴⁶



A useful extension of Dieckmann's method involves the condensation of oxalic ester with other esters of dibasic acids. In the case of glutaric esters the product is 1,2-cyclopentanedione.

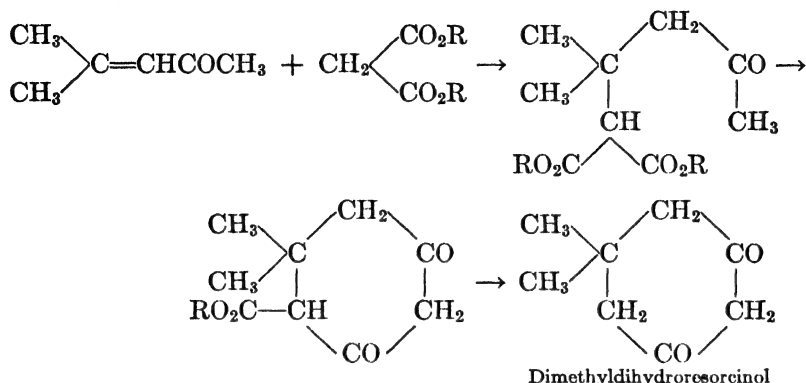


It was this special method which enabled Komppa to synthesize camphoric acid and thus to establish conclusively the structure of camphor. The steps in this celebrated synthesis are as follows:

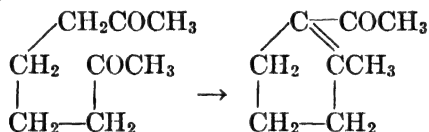


⁴⁶ Hudson and Hauser, *J. Am. Chem. Soc.*, **61**, 3567 (1939).

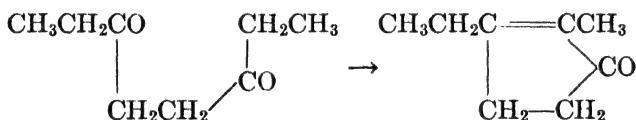
Another group of syntheses of this general type depends on the Michael condensation; it may be illustrated by the preparation of dimethyldihydroresorcinol from mesityl oxide and malonic ester.⁴⁷



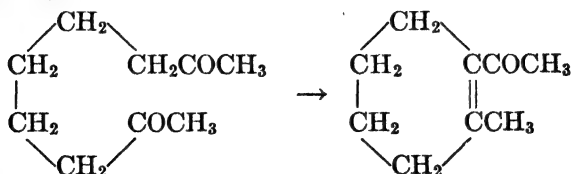
Cyclodehydration. Condensations of the aldol type involving loss of water have been widely used in the synthesis of ring compounds. Thus, 2,7-octanedione is converted by the action of sulfuric acid into a cyclopentene derivative.⁴⁸



Similarly, 3,6-octanedione yields a cyclopentenone when treated with 10 per cent potassium hydroxide solution.⁴⁹



It is to be noted that in both these examples the course of the reaction is determined by the size of the ring formed; the formation of a five-membered ring is favored over that of a three- or a seven-membered ring. Similarly, Kipping and Perkin found that the six-membered ring forms in preference to the eight-membered ring, as shown by the fact that 2,8-nonanedione gives exclusively a cyclohexene-derivative.

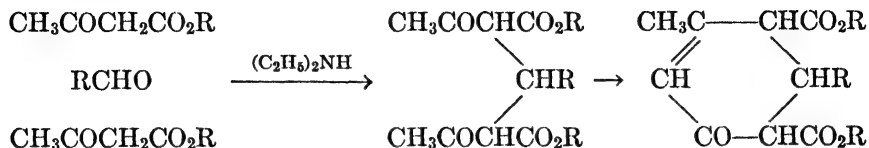


⁴⁷ Vorländer and Erig, *Ann.*, **294**, 314 (1897).

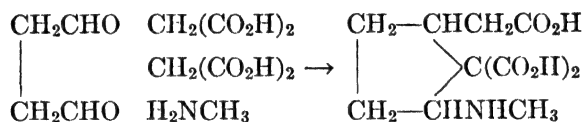
⁴⁸ Marshall and Perkin, *J. Chem. Soc.*, **57**, 241 (1890).

⁴⁹ Blaise, *Compt. rend.*, **158**, 708 (1914).

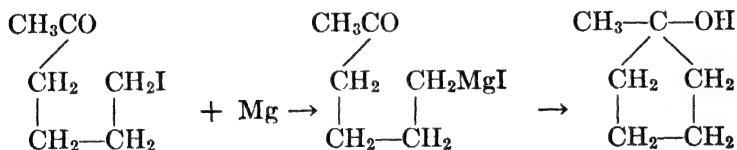
Alkylidene derivatives resulting from the use of Knoevenagel's method are capable of internal condensations leading to the formation of rings. The use of aldehydes and acetoacetic ester, for example, leads to the formation of cyclohexenone derivatives.



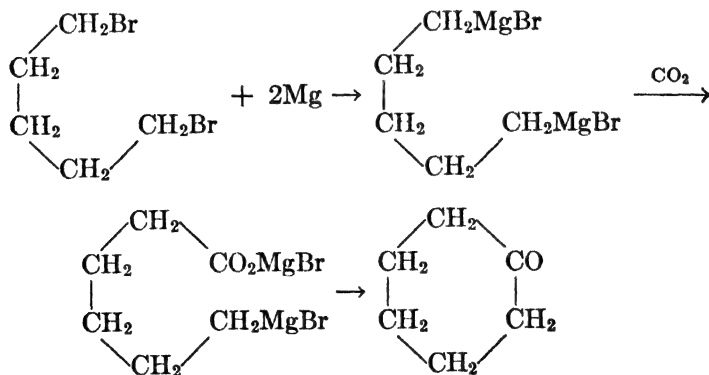
Another type of ring closure is represented by the condensation of succinic dialdehyde, methylamine, and malonic acid in the following manner:⁵⁰



The Grignard Method (p. 495). Certain halogen compounds form Grignard reagents which condense internally to give ring structures. Thus, 6-iodo-2-hexanone reacts with magnesium to give 1-methylcyclopentanol. A Grignard reagent is formulated as an intermediate.⁵¹



Similarly, pentamethylene bromide when treated with magnesium and then with carbon dioxide gives, in addition to pimelic acid, a small yield of cyclohexanone.⁵²

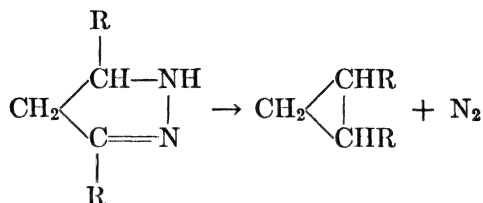


⁵⁰ Mannich and Budde, *Arch. Pharm.*, **270**, 283 (1932).

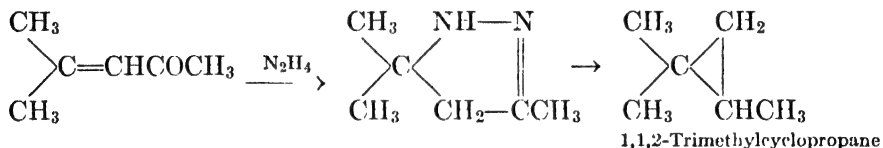
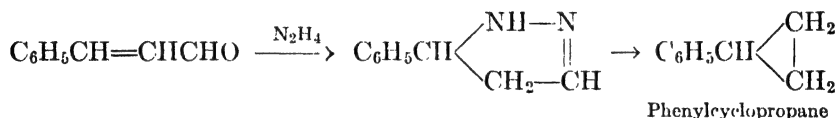
⁵¹ Zelinsky and Moser, *Ber.*, **35**, 2684 (1902).

⁵² Grignard and Vignon, *Compt. rend.*, **144**, 1358 (1907).

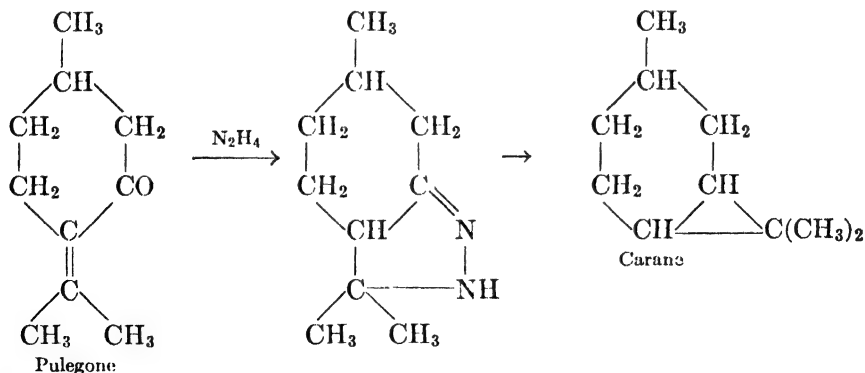
Pyrolysis of Pyrazolines. Pyrazolines are unstable toward heat and decompose to give cyclopropane derivatives.



α,β -Unsaturated ketones and aldehydes yield pyrazolines when treated with hydrazine and can be converted by this method into the corresponding cyclopropane derivatives. Thus, cinnamic aldehyde gives phenylcyclopropane, and mesityl oxide yields 1,1,2-trimethylcyclopropane.



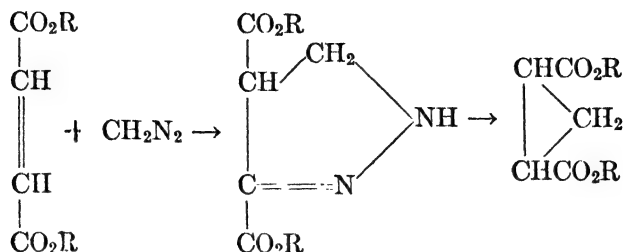
A classical example of this type of reaction is Kishner's conversion of pulegone into carane.⁵³



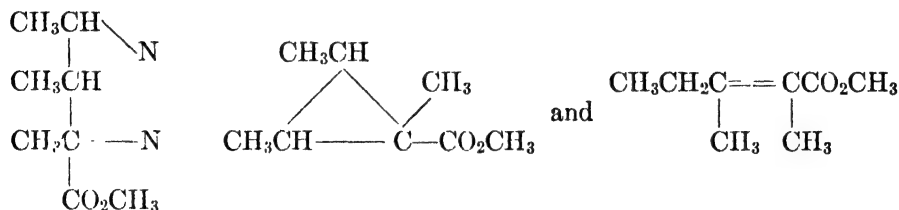
Alkyl pyrazolinecarboxylates are readily made by the action of diazomethane on unsaturated esters such as those of maleic, fumaric, and crotonic acids. It is interesting to note that maleic and fumaric esters

⁵³ Kishner and Zavadovsky, *J. Russ. Phys. Chem. Soc.*, **43**, 1132 (1911).

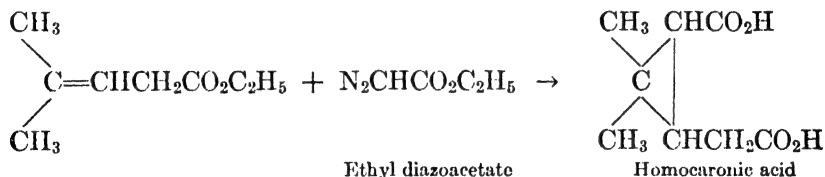
give the same pyrazoline; from these esters alkyl 1,2-cyclopropanedicarboxylates are made.



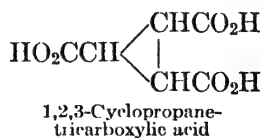
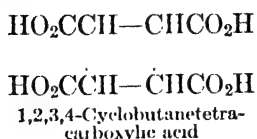
Thermal decomposition of the simple pyrazoline derivatives usually gives alkyl alkenecarboxylates as the main product; the more complex esters generally afford a preponderance of alkyl cyclopropanecarboxylates. Mixtures of the two types of products are often formed; the following illustrates this behavior:⁵⁴



Diazoacetic ester has been used in a similar fashion. For example, homocaronic acid was prepared by the action of the diazo ester on ethyl 4-methyl-3-pentenoate.⁵⁵



A by-product in this reaction is 1,2,3,4-cyclobutanetetracarboxylic acid, obviously derived from four molecules of the diazo ester. The analogous 1,2,3-cyclopropanetricarboxylic acid results when maleic ester is used.

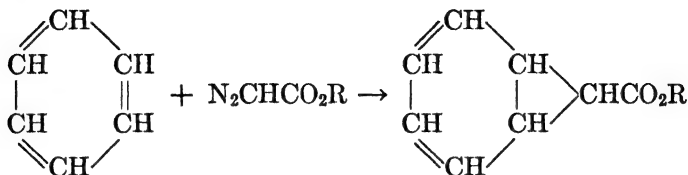


As a side light on the influence of substituents on stability it may be pointed out that carboxyl groups, when situated on different carbon

⁵⁴ v. Auwers and König, *Ann.*, **496**, 252 (1932).

⁵⁵ Owen and Simonsen, *J. Chem. Soc.*, 1225 (1933).

atoms of these small rings, greatly enhance the stability. The conversion of ethylenic compounds into cyclopropane derivatives by the diazoacetic ester method is very general. Büchner has shown that even aromatic rings are attacked. Benzene is transformed in the following fashion:

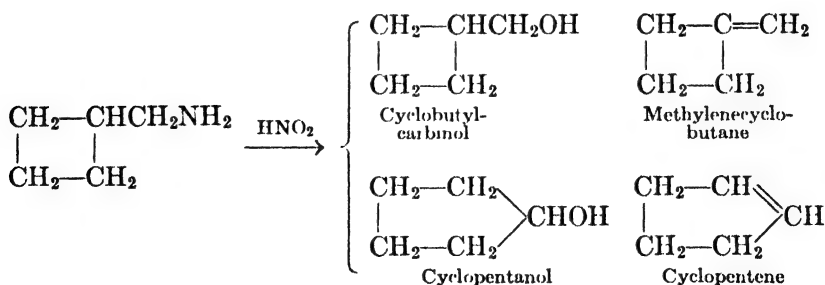


Oxidation converts the above product into 1,2,3-cyclopropanetricarboxylic acid.

METHODS OF RING EXPANSION AND CONTRACTION

Many reactions of alicyclic compounds produce a change in the size of the ring. These are of particular interest from the standpoint of the strain theory, which carries the implication that such transformations have as their driving force a diminution of ring tension. In support of this may be cited numerous examples of expansion of the smaller (strained) rings and of contraction of large rings, and it was believed that these constitute strong evidence for the soundness of Baeyer's original theory. However, a more careful study of such changes has shown that they cannot be correlated in any simple way with the strain which the rings are supposed to possess. Some examples will serve to indicate the difficulties involved.

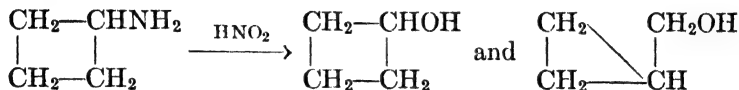
The Demjanow Rearrangement. The action of nitrous acid on cycloalkylmethanamines is a general method for ring expansion. Cyclobutylmethanamine will illustrate the behavior of this class of amines. In general, four products are obtained; in this instance they are cyclopentanol, cyclopentene, cyclobutylcarbinol, and methylenecyclobutane.



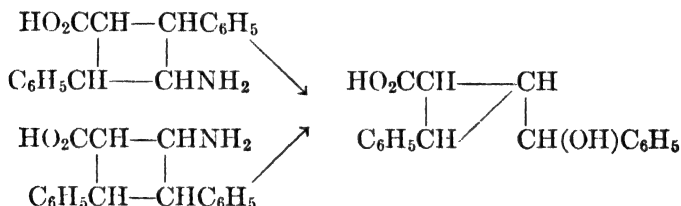
The three-, five-, six-, and eight-membered rings have also been transformed in this way. Obviously, ring strain is not the primary cause of

this change, for it proceeds with especial readiness in the case of cyclohexylmethylamine (60 per cent yield). Also, Ruzicka has shown that the rearrangement from the cycloöctyl to the cyclononyl ring gives a 20 per cent yield of cyclononanol; here the rearrangement can hardly be ascribed to strain alone.

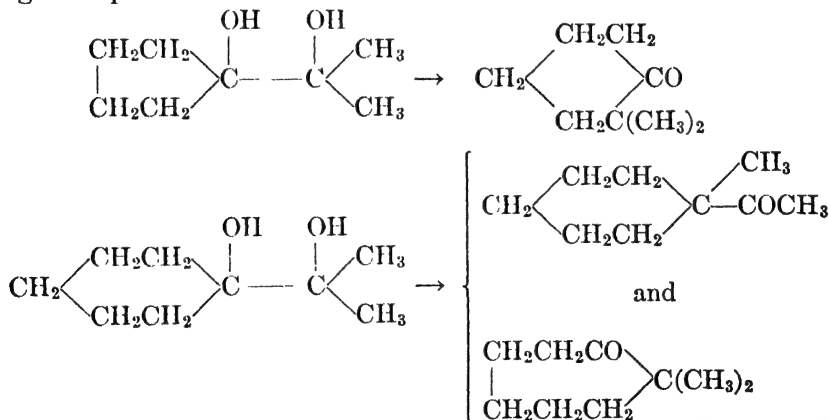
Equally difficult to correlate with the strain theory is the ring contraction which cyclobutylamines undergo when treated with nitrous acid. In addition to the normal cyclobutanol some cyclopropylcarbinol results.



The cyclobutylamines derived from truxinic and truxillic acids undergo a similar change.⁵⁶



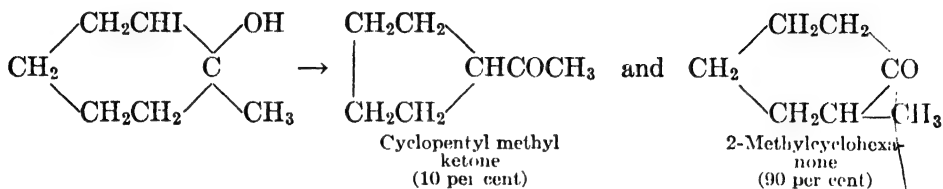
The Pinacol-Pinacolone Rearrangement (p. 971). The rearrangement of cyclic pinacols has been shown by Meerwein to obey the general rules known to hold for acyclic pinacols. Attention is directed to the following examples:



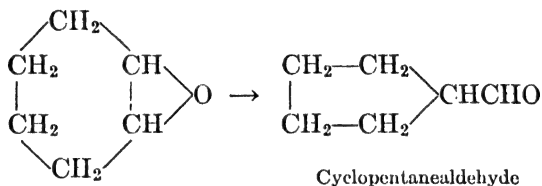
The fact that expansion of the cyclohexane ring is less complete than that of the cyclopentane ring in these cases may be an indication that a resistance is encountered in the former which is not present in the latter. This accords with the strain theory in its original form.

⁵⁶ Stoermer, Schenck, and Pansegrau, *Ber.*, **60B**, 2566 (1927).

A number of transformations have been observed which appear to be closely related to the pinacol-pinacolone rearrangement. Many of these involve a change of a six- to a five-membered ring, and so serve to complicate the problem of correlating such changes with ring size. Treatment with silver nitrate converts 1-methyl-2-iodocyclohexanol into cyclopentyl methyl ketone. However, the primary product is 2-methylcyclohexanone.⁵⁷



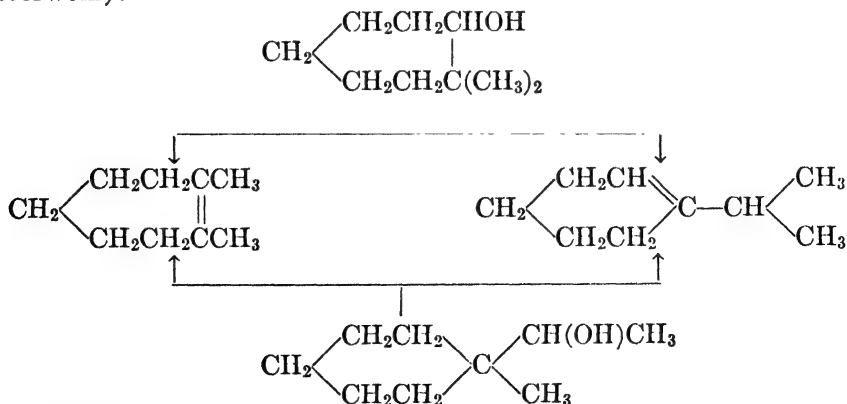
Similarly, cyclohexene oxide, when treated with magnesium bromide in ether solution, is converted into cyclopentanealdehyde.



However, under the same conditions cyclopentene oxide does not yield a cyclobutane derivative, but rearranges to cyclopentanone.⁵⁸

The Wagner Rearrangement (p. 1019). The dehydration of cyclic

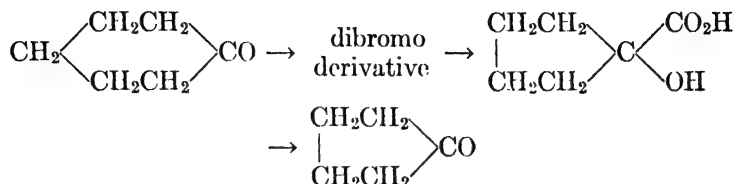
alcohols containing the $\begin{array}{c} \text{C} \\ | \\ \text{C} - \text{C} - \text{C}(\text{OH}) \\ | \\ \text{C} \end{array}$ grouping may produce either expansion or contraction of the ring, as shown by the following examples (Meerwein):



⁵⁷ Tiffeneau, *Compt. rend.*, **195**, 1284 (1932).

⁵⁸ Clemo and Ormston, *J. Chem. Soc.*, 362 (1933).

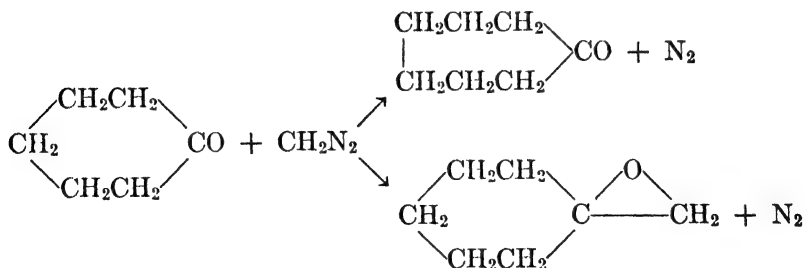
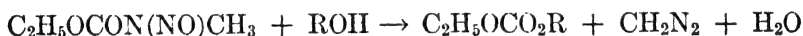
Wallach's Degradation Method. Cyclohexanones can be converted to the corresponding cyclopentanones by the method of Wallach, which involves the treatment of the dibromocyclohexanone with alkali. The 1-hydroxycyclopentanecarboxylic acid is always an intermediate.



Favorski reported a similar result with α -chlorocyclohexanones, which are converted by alkali into cyclopentanecarboxylic acids.



The Diazomethane Method. Diazomethane is capable of reacting with aldehydes and ketones in such a manner as to produce the higher homologs. Mosettig and Burger⁵⁹ applied this method to cycloalkanones and found that cyclohexanone gave a mixture of cycloheptanone and cycloöctanone of which the former was the principal product. From cyclopentanone the chief product was cycloheptanone. More recently⁶⁰ the method has been adapted to large-scale operation by introducing nitrosomethylurethan at a suitable rate into a solution of a cyclic ketone in an alcohol which contains some alkaline catalyst. The chief reactions in the case of cyclohexanone may be represented by the following equations, although the actual intermediate is not necessarily diazomethane.



The ratio of ketone to oxide is in general about four to one.

⁵⁹ Mosettig and Burger, *J. Am. Chem. Soc.*, **52**, 3456 (1930); see also Robinson and Smith, *J. Chem. Soc.*, 371 (1937), and Giraitis and Bullock, *J. Am. Chem. Soc.*, **59**, 951 (1937).

⁶⁰ Meerwein, *Chem. Zentr.*, **104**, II, 1758 (1933) (German pat. 579,309).

With this method the yield of ketone falls from 63 per cent in the preparation of cycloheptanone to 45 per cent for the octanone and to about 20 per cent for the nonanone and decanone.⁶¹ In this range the diazomethane method seems to be superior to all others for the synthesis of cyclic ketones.

It has been reported that the yields increase with higher members so that in the range of the cyclopentadecanone the method is again to be preferred.

The reaction does not, of course, stop when one methylene group has been introduced and therefore yields a mixture of ketones. This is illustrated by the action of diazomethane on ketene (cycloethanone).

In an attempt to use this method in the preparation of cyclopropanone by treating ketene (cycloethanone) with diazomethane it was found that the chief product was cyclobutanone; presumably the cyclopropanone is an intermediate.^{62, 63} By using an excess of ketene with diazomethane it was possible to isolate the hydrate and some hemiacetals of cyclopropanone.

In addition to the foregoing examples of ring expansion and contraction may be mentioned the conversion of the cyclopropyl- and cyclobutylcarbinols to cyclobutyl and cyclopentyl bromide, respectively, by the action of hydrogen bromide; the rearrangement of cyclopentyl nitrite to 1-methylnitrocyclobutane under the influence of alkali; the formation of methylecyclopentane by the reduction of benzene with hydrogen iodide at 300°; the transformation of carbazole into 3,3'-dimethyldicyclopentyl by the action of hydrogen iodide;⁶⁴ the reversible formation of methylecyclopentane from cyclohexane in the presence of moist aluminum chloride; and the transformation of pinene into bornyl chloride under the influence of hydrogen chloride.

As has been stated, the foregoing transformations lend themselves to no simple explanation such as that offered by Baeyer. Indeed, most of them find their counterpart in the reactions of open-chain compounds in which strain in the Baeyer sense cannot be involved. It appears at present that the small rings are indeed strained; but it is equally evident that strain is not always the controlling factor and that frequently it is entirely obscured by other influences.

⁶¹ Kohler, Tishler, Potter, and Thompson, *J. Am. Chem. Soc.*, **61**, 1057 (1939).

⁶² Lipp, Buchkremer, and Seeles, *Ann.*, **499**, 1 (1932).

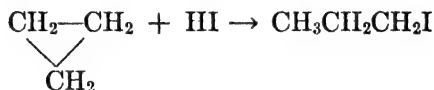
⁶³ Lipp and Köster, *Ber.*, **64B**, 2823 (1931).

⁶⁴ Schmidt and Sigwart, *Ber.*, **45**, 1779 (1912).

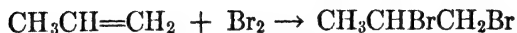
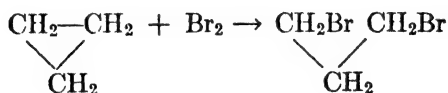
METHODS OF OPENING RINGS

Alicyclic rings in general exhibit a stability toward heat and reagents which is comparable to that of the corresponding open-chain compounds. Only in cyclopropane and its derivatives, and, to a far less degree, cyclobutane and its derivatives, is there any marked instability. Even so, the stability of related compounds is exceedingly variable. Consequently, for a proper appreciation of the chemical behavior of the three- and four-membered ring systems it is necessary to examine their properties in some detail.

Cleavage of the Cyclopropane Ring. The close resemblance in chemical behavior of cyclopropane and its derivatives to the corresponding olefinic compounds has already been mentioned. This point of view offers the most helpful approach to an appreciation of the manner in which the cyclopropane ring is opened by heat and by reagents. Cyclopropane and its derivatives are unstable toward heat, which converts them to the corresponding propylene derivatives. Cyclopropane is readily reduced to propane by the action of hydrogen in the presence of colloidal palladium in acetic acid solution; under the same conditions ethylene is reduced somewhat more rapidly. Hydrogen iodide adds readily to cyclopropane to give *n*-propyl iodide. Under these conditions propylene gives principally isopropyl iodide.



Bromine adds to cyclopropane just as it does to propylene, but the reaction is slower and the product is the 1,3-dibromide instead of propylene bromide.



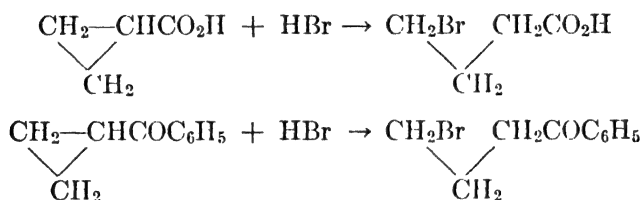
Whereas cyclopropane in these reactions is almost as unsaturated as propylene, it differs notably from the latter in being stable toward permanganate and ozone.

The ease with which the ring opens, i.e., the ease with which addition takes place, is greatly affected by the nature and position of substituents. Alkyl groups seem to decrease the stability of the ring. Carboxyl groups, on the other hand, seem to stabilize the ring, and this

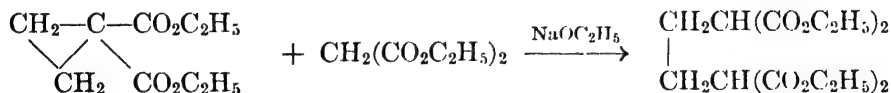
effect, as has already been noted (p. 95), is the more marked if these groups are on different carbon atoms.

Although the influence of substituents on the *ease of addition* cannot as yet be interpreted in any helpful way, the effect of substituents on the *mode of addition* is predictable on the basis of the rule of Markownikoff (p. 638). The problem has been carefully examined by Kohler and Conant,⁶⁵ who state that substituents have exactly the same influence upon the mode of addition to a cyclopropane ring as to an ethylenic linkage, even though the resulting saturated derivatives in the two instances differ radically in structure. For example, the manner in which hydrogen bromide adds to cyclopropane hydrocarbons is governed by the number and disposition of the alkyl groups. The ring invariably opens between the carbon atoms that hold the largest and the smallest number of alkyl groups, and the principal product is always one in which the halogen is combined with the carbon atom that holds the largest number of alkyl groups.

The addition of hydrogen bromide to cyclopropane acids leads to the formation of γ -bromo acids or the corresponding lactones. The ketones behave in a similar manner. Cyclopropanecarboxylic acid and benzoylcyclopropane are examples of this sort; with hydrogen bromide they react as follows:



Similarly, ethyl 1,1-cyclopropanedicarboxylate undergoes the Michael reaction with ethyl malonate to give ethyl 1,1,4,4-butanetetracarboxylate.⁶⁶



These facts justify the conclusion that there is no fundamental difference between corresponding derivatives of ethylene and cyclopropane, and that the structure $\begin{array}{c} \text{---C---} \quad \text{C---} \quad \text{C=O} \\ \diagup \quad \diagdown \\ \text{C} \\ \diagup \end{array}$ behaves like a conjugated system.

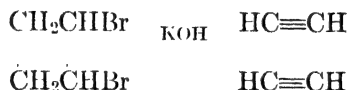
⁶⁵ Kohler and Conant, *J. Am. Chem. Soc.*, **39**, 1404 (1917).

⁶⁶ Bone and Perkin, *J. Chem. Soc.*, **67**, 108 (1895).

Cleavage of the Cyclobutane Ring. Cyclobutane is transformed into butane by catalytic hydrogenation at 120° , thus requiring somewhat more drastic treatment than cyclopropane which passes into propane under these conditions at 80° . On the other hand, cyclopentane is opened by catalytic hydrogenation only at 300° .⁶⁷ From the standpoint of the tendency to absorb hydrogen in the presence of a catalyst the simple cycloalkanes fall in the order ethylene > cyclopropane > cyclobutane > cyclopentane; this is, of course, in complete harmony with the requirements of strain theory.

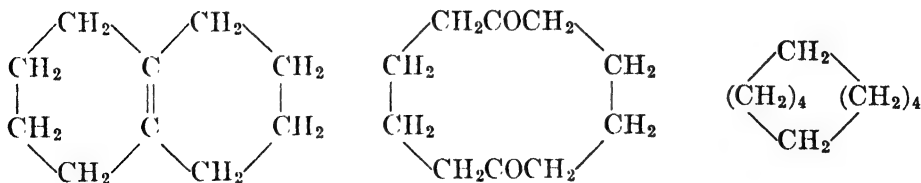
The type of rupture of this ring which is most frequently observed is a dissociation into two molecules of olefinic character. This was noted with respect to truxinic and truxillic acids which dissociate under the influence of heat to give cinnamic acid (p. 75).

When 1,2-dibromocyclobutane is heated with potassium hydroxide, acetylene is produced.



THE CYCLOALKANES

Saturated alicyclic hydrocarbons have usually been made by reduction of the corresponding ketones and diketones. Special methods, however, have been necessary in some instances, such as that for cyclopropane, which has already been discussed.* Cyclobutane is made by hydrogenation of cyclobutene in the presence of nickel at 100° . This process must be carefully controlled since at higher temperatures butane is formed. Cyclopentane, cyclohexane, and cycloheptane are found in petroleum. An interesting synthesis of cyclodecane has been worked out which involves the ozonization of octahydronaphthalene and reduction of the resulting diketone.⁶⁸



The following table gives the boiling points, melting points, and heats

⁶⁷ Zelinsky, Kazansky, and Plate, *Ber.*, **66B**, 1415 (1933).

* Cyclopropane has attracted much attention because of its value as a general anesthetic

⁶⁸ Hückel, Gereke, and Gross, *Ber.*, **66B**, 563 (1933).

of combustion of a representative group of cycloalkanes. The last column gives for comparison the boiling points of the corresponding paraffins.

CYCLOALKANES

| Name | Heat of Combustion per CH ₂ (Cal.) | Melting Point | Boiling Point | |
|---|---|---------------|---------------|-----------|
| | | | Cycloalkanes | Paraffins |
| Ethylene (cycloethane).... | 170 | | -103 9° | -84 1° |
| Cyclopropane..... | 168.5 | | -35 | -44 5 |
| Cyclobutane..... | 165.5 | | +12 | -0.1 |
| Cyclopentane..... | 159 | | 49 | +36.2 |
| Cyclohexane..... | 158 | +7° | 81 | 68.9 |
| Cycloheptane..... | 158 | - 12 | 117 | 98.8 |
| Cycloöctane..... | | +11 5 | 148 | 125 8 |
| Cyclodecane (C ₁₀ H ₂₀).... | 158 6 | 9 6 | 201 | 173 |
| Cyclododecane (C ₁₂ H ₂₄)... | | 61 | | |
| Cyclotetradecane (C ₁₄ H ₂₈).. | | 53 | | |
| Cyclopentadecane (C ₁₅ H ₃₀).. | 157 | 37 | | |
| Cyclohexadecane (C ₁₆ H ₃₂).. | | 57 | | |
| Cycloheptadecane (C ₁₇ H ₃₄).. | 157 | 63 | | |
| Cyclodocosane (C ₂₂ H ₄₄)... | | 46 | | |
| Cyclotetracosane (C ₂₄ H ₄₈).. | | 47 | | |
| Cyclohexacosane (C ₂₆ H ₅₂).. | | 42 | | |
| Cycloöctacosane (C ₂₈ H ₅₆).. | | 48 | | |
| Cyclotriacontane (C ₃₀ H ₆₀).. | 156 | 56 | | |

It is clear that the values given for the energy content of the cycloparaffins fully support the modern interpretation of the strain theory, which holds that all the rings of more than four members are practically without strain. They furnish no evidence of strain in cyclohexane and cycloheptane which, according to Baeyer, should possess negative strain. Moreover, the heats of combustion of large rings, varying in size from eight to thirty members, are now known, and, although the accuracy of the measurements leaves much to be desired, it is evident that the values of the heat of combustion of a CH₂ group in these rings agree throughout with the corresponding values for the aliphatic compounds and the homologous cyclopentanes and cyclohexanes.⁶⁹

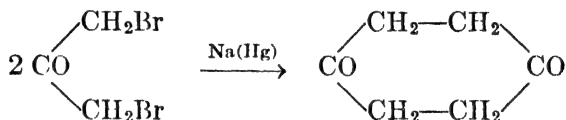
The parachors as well as the compressibilities of the cycloalkanes have been measured, and it has been shown that these properties, like stability, molecular refractivity, molecular volume, specific gravity,

⁶⁹ Ruzicka and Schläpfer, *Helv. Chim. Acta*, **16**, 162 (1933).

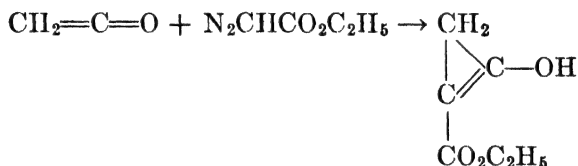
melting point, and x-ray structure (p. 1762)—abnormal for the lower members—become “normal” for the compounds with the larger rings.⁷⁰

THE CYCLOALKANONES

Cyclopropanone is known only in the form of its hydrate and alcoholates.⁶² Efforts to synthesize this ketone have already been noted (p. 100). Also, treatment of dibromoacetone with sodium amalgam gives 1,4-cyclohexanedione instead of cyclopropanone.



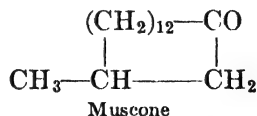
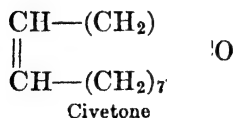
By the action of ethyl diazoacetate on ketene, Staudinger prepared a compound which appears to be the enol form of a derivative of cyclopropanone.



Cyclobutanone has been made by the oxidation of cyclobutanol and also by treating 1-bromocyclobutanecarboxamide with bromine in potassium hydroxide. Its synthesis from ketene by the action of diazomethane has already been mentioned (p. 100).

The higher cycloalkanones have usually been prepared by direct cyclization by reactions which were discussed under methods of ring closure.

Cyclopentadecanone is of especial interest on account of its musk-like odor; it is sold as a perfume under the name “exaltone.” It is similar in structure to the odoriferous principles of naturally occurring civet and musk. The former contains civetone and the latter muscone. Ruzicka’s



establishment of the structures of these two naturally occurring alicyclic compounds is one of the most significant achievements in this field,

⁷⁰ Ruzicka, Boekenoogen, and Edelman, *ibid.*, **16**, 487 (1933).

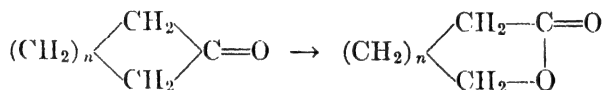
CYCLOALKANONES

| Name | Formula | Melting Point | Boiling Point |
|----------------------|---|---------------|-------------------|
| Cyclobutanone..... | $\begin{array}{c} \text{CH}_2-\text{CO} \\ \quad \\ \text{CH}_2-\text{CH}_2 \end{array}$ | | 98.5-99° |
| Cyclopentanone.... | $\begin{array}{c} \text{CH}_2\text{CH}_2 \\ \quad \diagup \\ \text{CH}_2\text{CH}_2 \end{array} \text{CO}$ | | 130-130.5 |
| Cyclohexanone..... | $\text{CH}_2 \begin{array}{c} \diagup \text{CH}_2\text{CH}_2 \\ \diagdown \text{CH}_2\text{CH}_2 \end{array} \text{CO}$ | | 155.4 |
| Cycloheptanone..... | $(\text{CH}_2)_4 \begin{array}{c} \diagup \text{CH}_2 \\ \diagdown \text{CH}_2 \end{array} \text{CO}$ | | 179-181 |
| Cycloöctanone..... | $(\text{CH}_2)_5 \begin{array}{c} \diagup \text{CH}_2 \\ \diagdown \text{CH}_2 \end{array} \text{CO}$ | 42° | 74 (12 mm.) |
| Cyclononanone..... | $\begin{array}{c} \text{CH}_2-(\text{CH}_2)_3 \\ \quad \diagup \\ \text{CH}_2-(\text{CH}_2)_3 \end{array} \text{CO}$ | | 93-95 (12 mm.) |
| Cyclodecanone.... | $\text{CH}_2 \begin{array}{c} \diagup (\text{CH}_2)_4 \\ \diagdown (\text{CH}_2)_4 \end{array} \text{CO}$ | 29 | 100 (12 mm.) |
| Cyclododecanone. . | $\text{CH}_2 \begin{array}{c} \diagup (\text{CH}_2)_5 \\ \diagdown (\text{CH}_2)_5 \end{array} \text{CO}$ | 59 | 125 (12 mm.) |
| Cyclotetradecanone . | $\text{CH}_2 \begin{array}{c} \diagup (\text{CH}_2)_6 \\ \diagdown (\text{CH}_2)_6 \end{array} \text{CO}$ | 53 | 155 (12 mm.) |
| Cyclopentadecanone . | $\begin{array}{c} \text{CH}_2-(\text{CH}_2)_6 \\ \quad \diagup \\ \text{CH}_2-(\text{CH}_2)_6 \end{array} \text{CO}$ | 63 | 120 (0.3 mm.) |
| Cyclohexadecanone . | $\text{CH}_2 \begin{array}{c} \diagup (\text{CH}_2)_7 \\ \diagdown (\text{CH}_2)_7 \end{array} \text{CO}$ | 64 | 138 (0.3 mm.) |
| Cyclocosanone..... | $\text{CH}_2 \begin{array}{c} \diagup (\text{CH}_2)_9 \\ \diagdown (\text{CH}_2)_9 \end{array} \text{CO}$ | 59 | 170-171 (0.3 mm.) |
| Cyclodocosanone ... | $\text{CH}_2 \begin{array}{c} \diagup (\text{CH}_2)_{10} \\ \diagdown (\text{CH}_2)_{10} \end{array} \text{CO}$ | 32 | |
| Cycloöctacosanone .. | $\text{CH}_2 \begin{array}{c} \diagup (\text{CH}_2)_{11} \\ \diagdown (\text{CH}_2)_{11} \end{array} \text{CO}$ | 54 | |

for it dispelled the fallacy that large rings were incapable of existence, and opened up an entirely new field of investigation. This work constitutes a remarkable instance of the great theoretical and practical developments which frequently grow out of the study of natural products.

The chemical properties of the cycloalkanones are, in general, similar to those of open-chain ketones. The lower members of the cyclic series, however, are much more reactive toward typical ketone reagents than are the corresponding members of the open-chain group. Thus, whereas, in general, only methyl ketones will form bisulfite addition compounds, this reaction is observed for all the cycloalkanones up to and including cycloöctanone. Cycloöctanone can be separated from cyclononanone by making use of this difference. It must be supposed that, in the smaller rings, the ring form leaves the carbonyl group more exposed to the attack of reagents than in the open-chain forms or the very large rings.

A reaction which is of great interest is the oxidation of cycloalkanones to the corresponding lactones by the use of Caro's acid.

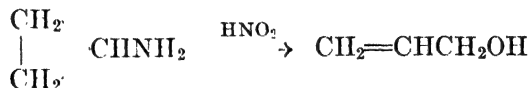


The reaction was discovered by Baeyer and Villiger,⁷¹ and has proved to be very general. In this way, the lactones in which $n = 10, 11, 12, 13$, and 14 have been obtained in yields of about 50 per cent of the theoretical amount.⁷²

The table on page 106 gives the boiling points and melting points of a number of the cycloalkanones.

THE CYCLOALKANOLS AND CYCLOALKANEDIOLS

Cyclopropanol is not known; efforts to prepare it invariably lead to the formation of the isomeric open-chain compound, allyl alcohol.⁷³ Thus, this alcohol is produced when nitrous acid is allowed to react with cyclopropylamine.



It should be pointed out that this is a Demjanow rearrangement in which a two-membered ring is derived from a three-membered ring. Cyclobutanol, the synthesis of which has already been mentioned (p. 97), is,

⁷¹ Baeyer and Villiger, *Ber.*, **32**, 3625 (1899); **33**, 862 (1900).

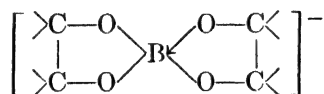
⁷² Ruzicka and Stoll, *Helv. Chim. Acta*, **11**, 1159 (1928).

⁷³ Hurd and Pilgrim, *J. Am. Chem. Soc.*, **55**, 1195 (1933).

however, a relatively stable substance and resembles *n*-butyl alcohol very closely in its chemical and physical properties.

Cyclohexanol is the only cycloalkanol which is available in commercial quantities. It is made by catalytic hydrogenation of phenol in the presence of nickel at about 170°. It gives the usual reactions of secondary alcohols. Gentle oxidation converts it into cyclohexanone, and vigorous treatment gives adipic acid.

The 1,2-Cycloalkanediols. The 1,2-cycloalkanediols are of especial interest because of their behavior toward boric acid and acetone. Böeseken⁷⁴ has found that certain polyols, when introduced into a solution of boric acid, enhance its conductivity. This effect is ascribed to the formation of addition complexes. These complexes are formulated as borospiranic acids, of which the anions are borospirans of the following type:



Apparently such complexes form only when the polyol molecule holds two hydroxyl groups which are close together. This criterion of the proximity of hydroxyl groups in glycols has given rise to numerous experiments, the results of which seem to support the theory that the cyclohexane ring is less rigid than those of the lower cycloalkanes. Ethylene glycol does not increase the conductivity of boric acid solutions, apparently because the mutual repulsion of the hydroxyl groups causes the molecule to rotate so as to allow these groups to take up positions which are far apart. A similar result is obtained with *trans*-1,2-cyclopentanediol in which the hydroxyl groups, owing to the absence of free rotation about the line joining the carbon atoms holding them, cannot come close together (see Fig. 5b). Confirmation of this view is seen in the fact that *cis*-1,2-cyclopentanediol (Fig. 5a) greatly increases the conductivity. Here the hydroxyl groups are close together and, on account of the rigidity of the ring, cannot move. Similar results have been obtained with substituted cyclopentane-1,2-diols and the hydrindene-1,2-diols (Fig. 5c). (See p. 444 for a general discussion of *cis-trans* isomerism.)

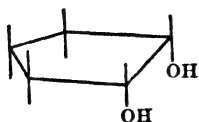


FIG. 5a

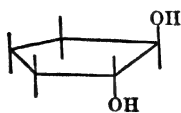


FIG. 5b

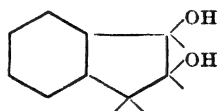


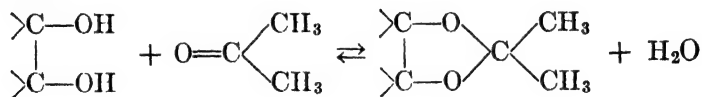
FIG. 5c

⁷⁴ Böeseken, *Inst. intern. chim. Solvay, Conseil chim. 4th Conseil, Brussels* (1931)

The behavior of the *cis*- and *trans*-1,2-cyclohexanediols furnishes striking evidence for the theory that these rings are non-planar, for neither of these glycols increases the conductivity. This would, of course, be the expected result for the *trans* form even if the ring were planar; but the fact that the *cis* glycol does not increase the conductivity shows that the hydroxyl groups here are able to move apart owing to the flexibility of the ring. Only the non-planar ring possesses such flexibility.

The formation of five-membered rings of a somewhat similar nature has been postulated by Criegee, Kraft, and Rank,⁷⁵ to explain the results obtained in the oxidative cleavage of 1,2-glycols with lead tetraacetate. They assume the intermediate formation of a heterocyclic ring containing lead. To the formation of this ring are attributed two experimentally observed facts: first, that the reaction velocity for a *cis*-glycol is much greater than that for a *trans*-glycol; and, second, that the ratio of the reaction velocity of a *cis* five-membered cyclic glycol to that of a *trans* five-membered cyclic glycol is larger than the similar ratio for *cis* and *trans* six-membered cyclic glycols. This latter fact indicates that the atoms of a six-membered ring do not lie in one plane.

Glycols tend to form cyclic acetals with acetone according to the following equation: ⁷⁶



The tendency of this reaction to go is taken as a measure of the proximity of the hydroxyl groups. As would be expected, in the case of *cis*-1,2-cyclopentanediol and the *cis*-indanediol the equilibrium lies far to the right. On the other hand, the *trans* forms give no acetals.

1,2-Glycols of the cyclohexane and tetralin series give results which resemble those obtained with boric acid. The *trans* forms give no derivatives with acetone, and in the *cis* forms the equilibrium lies far to the left. These results would appear to demonstrate that the cyclohexane ring is more flexible than the cyclopentane ring. However, the behavior of the 1,2-cycloheptanediols is not so easily explained on the basis of relative flexibilities of the rings. For here both the *cis* and *trans* modifications readily form acetals with acetone. Moreover, both forms increase the conductivity of boric acid, the effect of the *cis* form being about three times as great as that of the *trans*. The assumption, as yet unproved, that the cyclohexane ring possesses a greater flexibility than the smaller rings leads to the prediction that these glycols should have

⁷⁵ Criegee, Kraft, and Rank, *Ann.*, **507**, 159 (1933).

⁷⁶ Maan, *Rec. trav. chim.*, **48**, 332 (1929).

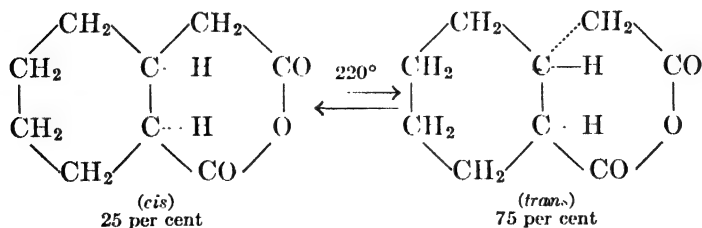
less effect than the corresponding cyclohexanediols. No completely satisfactory explanation of these results has been offered.

ALICYCLIC ACIDS

The monocarboxylic acids of this series present few problems which have not already been encountered in the open-chain series. The introduction of a second carboxyl group, however, gives rise to geometrical isomerism if the two groups are on different carbon atoms. Thus, 1,2-cyclobutanedicarboxylic acid exists in *cis* and *trans* modifications. This type of acid is of great interest because of the relation between ring structure and the tendency toward anhydride formation.

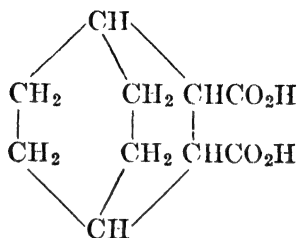
It is a well-established fact that 1,2-dicarboxylic acids, such as maleic and phthalic acids in which the carboxyl groups are near together, will form monomeric anhydrides, whereas similar acids in which the groups are far apart, as in fumaric and dimethylfumaric acids, do not form such anhydrides, at least not without first undergoing rearrangement. In the cyclobutane and cyclopentane series, the *cis*-1,2-dicarboxylic acids form monomeric anhydrides, whereas the corresponding *trans* forms fail to do so. From these results with open-chain dibasic acids, it seems clear that the formation of cyclic anhydrides is conditioned by the possibility of the carboxyl groups coming into close proximity to each other.

On the basis of this criterion, it is very significant that in the cyclohexane series *both* the *cis* and the *trans*-1,2-dicarboxylic acids form cyclic anhydrides. Examination of the models shows that only the strainless or non-planar forms possess sufficient flexibility to permit the carboxyl groups of *trans*-hexahydrophthalic acid to approach each other. Both the *cis* and *trans* modifications of hexahydroisophthalic acid form monomeric anhydrides with extreme ease. Hexahydrohomophthalic acid is especially interesting because *the anhydride of the trans form is more stable than that of the cis modification*. When either of the anhydrides is heated at 220° an equilibrium mixture is formed of which 75 per cent is the *trans* anhydride and 25 per cent the *cis* anhydride.³⁰

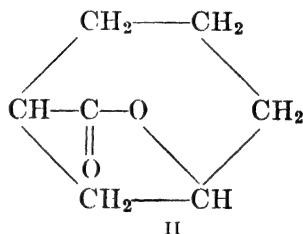
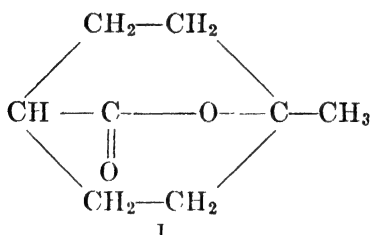


The correctness of the foregoing explanation of the formation of the monomeric anhydrides of *trans* modifications of acids of this type has

been confirmed by the synthesis of the endoethylene derivative of hexahydrophthalic acid, the *trans* form of which, though strainless, no longer possesses flexibility and, in consequence, cannot form a monomeric anhydride.



Many endocyclic bridges of this general type are known which, on the Baeyer theory, would involve strain but which can be represented as strainless if the non-planar cyclohexane ring is assumed. Among these are the lactones of *cis*-4-methyl-1-hydroxyhexahydrobenzoic acid (I),



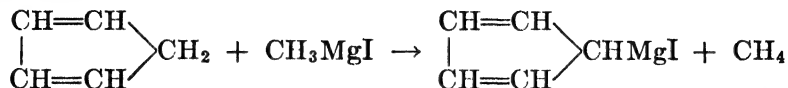
and of 3-hydroxyhexahydrobenzoic acid (II) and several of its homologs. Examples of this type have been greatly multiplied in recent years by use of the "diene" synthesis of Diels and Alder (p. 76). While the existence of compounds of the foregoing types seems difficult to reconcile with Baeyer's original theory, it is interesting to note that he was the first to observe the remarkable degree to which the hexahydrobenzene derivatives resemble the corresponding members of the paraffin series.

UNSATURATED ALICYCLIC COMPOUNDS

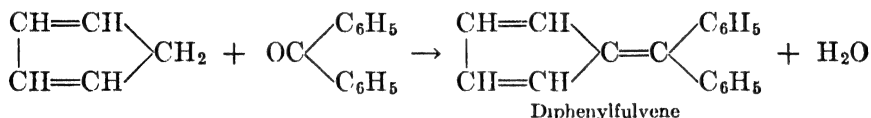
The cycloalkenes can ordinarily be prepared by the usual methods of making olefins, such as dehydration of the corresponding alcohols. However, owing to the instability of the rings, cyclopropene and cyclobutene require special methods. These have been synthesized from the corresponding bromides by thermal decomposition of the appropriate quaternary ammonium bases.

The simplest known cycloalkadiene is cyclopentadiene. It may be isolated from the fore-runings when crude benzene is distilled, and it has also been found among the decomposition products of heavy paraffin

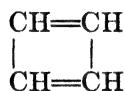
oil. Its tendency to polymerize has already been mentioned (p. 76). Cyclopentadiene is remarkable because it has an active methylene group. Thus, the diene reacts with methylmagnesium iodide to give a Grignard reagent and methane.



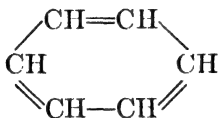
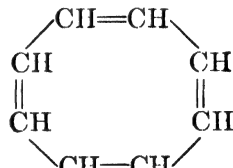
With aldehydes and ketones, cyclopentadiene condenses to give highly colored hydrocarbons known as *fulvenes*. Benzophenone, for example, leads to the formation of diphenylfulvene.



Cyclobutadiene has not been prepared. Particular interest attaches to this structure, however, because it is analogous to those of benzene (cyclohexatriene) and cyclooctatetraene in having a completely conjugated system. Cyclooctatetraene was found by Willstätter⁷⁷ to be



Cyclobutadiene

Cyclohexatriene
(benzene)

Cyclooctatetraene

highly unsaturated and entirely devoid of the properties peculiar to benzene and its derivatives. Because of the striking similarity between this compound and styrene in chemical and physical properties, the earlier work has been questioned.⁷⁸ Recently several investigators have attempted to find new routes to cyclooctatetraene derivatives.⁷⁹

From a consideration of the models it was expected that the introduction of a double bond into an alicyclic ring would render the ring less flexible and in small rings would introduce strain or augment that already present.

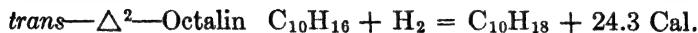
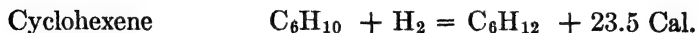
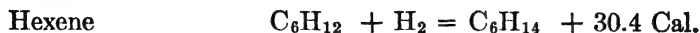
Some energy data are available relative to unsaturated compounds which offer support for the theory that a five-membered ring possesses

⁷⁷ Willstätter and Waser, *Ber.*, **44**, 3433 (1911); Willstätter and Heidelberger, *Ber.*, **46**, 517 (1913).

⁷⁸ Vincent, Thompson, and Smith, *J. Org. Chem.*, **3**, 603 (1939); Goldwasser and Taylor, *J. Am. Chem. Soc.*, **61**, 1260 (1939).

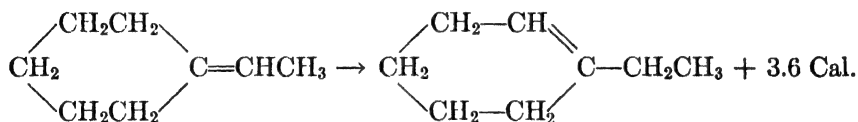
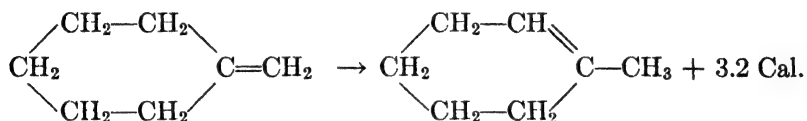
⁷⁹ Wawzonek, *J. Am. Chem. Soc.*, **62**, 745 (1940); Fry and Fieser, *ibid.*, **62**, 3489 (1940) Hurd and Drake, *ibid.*, **61**, 1943 (1939).

more strain than a six-membered ring, and that the six-membered ring, in turn, possesses less strain than the corresponding open-chain compound. The heats of hydrogenation show that a double bond is more stable in a six-membered ring than in an open-chain.



In support of this conclusion may be cited the fact that a double bond in a side chain will migrate to a six-membered ring, whereas the reverse has not been observed unless conjugation was involved.

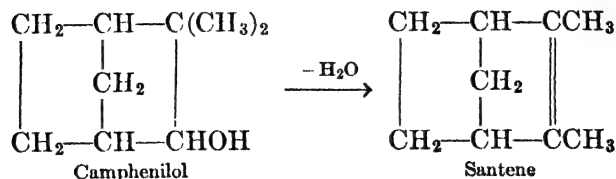
The magnitude of this tendency in the six-membered ring is indicated by the following heats of migration:



There is some evidence that the tendency for a semicyclic double bond to migrate to the ring is less in the five- than in the six-membered ring.

The cycloolefins have been found to react with phenyl azide, and the rate of this addition is believed to be a measure of the strain in the ring.⁸⁰ On this basis cyclopentene is much more strained than the higher members. If these data are correctly interpreted it follows that strainless unsaturated rings must contain more members than the corresponding saturated rings.

In this connection should be mentioned the Bredt rule, which relates to bridged rings. It states that in compounds of this type a carbon atom at a point of fusion of two rings cannot carry a double bond. Thus, dehydration of camphenilol does not give the normal unsaturated hydrocarbon, but yields santene instead.

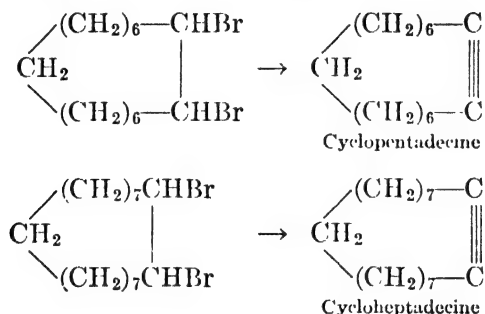


⁸⁰ Alder and Stein, *Ann.*, **501**, 1 (1933).

This rule has proved to be very general⁸¹ and has been interpreted to mean that such structures would involve a great amount of strain. If the ring system involved is strainless as in 9,10-octalin the rule no longer holds.

A special example of rings containing unsaturated linkages is furnished by the benzopolymethylene compounds. *o*-Benzopolymethylene rings are known varying in size from three members to rings of very large size. It is of interest to note, however, that the four-membered ring of this series has never been prepared. The *m*- and *p*-benzopolymethylene rings are very difficult to prepare. The only examples of this kind which are known contain rings of sixteen and seventeen members.⁸²

Rings are also known which contain the acetylene linkage.⁸³ Cyclopentadecine and cycloheptadecine have been made from the corresponding dibromides by treatment with alkali.



BICYCLIC COMPOUNDS

It is now believed that the cyclohexane ring is capable of existing in two forms (p. 321); from their shapes these are called the "saddle" and "chair" forms. Owing to the difficulty of separating these hypothetical stereoisomers, it is generally assumed that compounds possessing this ring pass readily from one form into the other.⁸⁴ It should be remarked, however, that in this transition the ring must be supposed to assume a form which involves a slight increase in the amount of strain. Proof of the existence of two such forms has come from studies of bicyclic ring systems. Several of these will be considered in some detail.

The simplest condensed ring system which may be regarded as strainless is that formed by the fusion of two cyclohexane rings in the 1,2 positions. Thus, according to the theory of Mohr (p. 69), decalin should exist

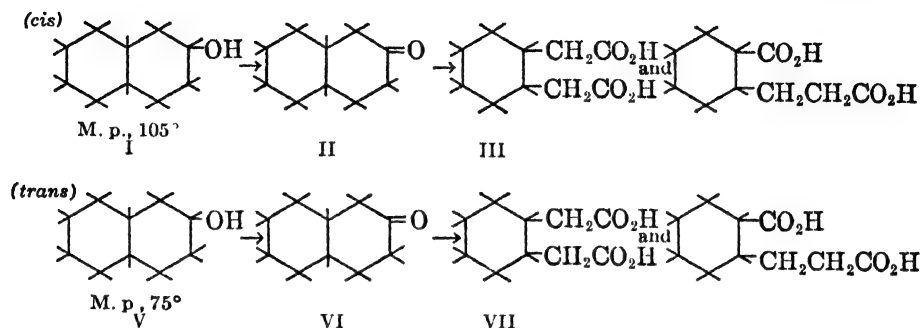
⁸¹ Brecht, *Ann.*, **437**, 1 (1924).

⁸² Ruzicka, Buijs, and Stoll, *Helv. Chim. Acta*, **15**, 1220 (1932).

⁸³ Ruzicka, Hürbin, and Bøkenoogen, *ibid.*, **16**, 498 (1933).

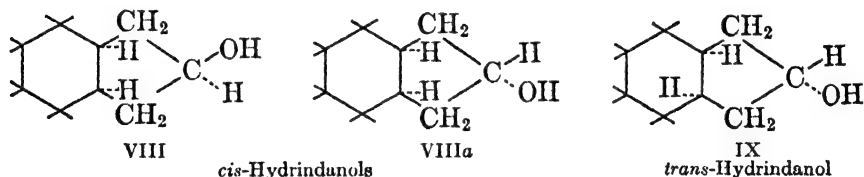
⁸⁴ Wightman, *J. Chem. Soc.*, 2541 (1926).

in *cis* and *trans* forms. In recent years Hückel has been able to demonstrate that this type of isomerism does occur in decalin and its derivatives. The β -decalols will serve to illustrate the type of evidence which supports this view.⁸⁵ β -Decalol (I) has been converted through the



decalone (II) to a cyclohexanedicarboxylic acid (III) which is known to have the *cis* configuration. This decalol, therefore, is a *cis* form. Similar degradation of the decalol melting at 75° (V) showed it to have the *trans* configuration. The acid VII is resolvable into optical antipodes and, thus, is proved to be the *trans* modification. The *cis* acid (III) is a *meso* form and cannot be resolved.

Isomerism of this type has been demonstrated for the α -decalols, the α - and β -decalylamines, and a number of other derivatives of decalin. A similar type of isomerism is known in the hydrindane series. The β -hydrindanol derived from III by ring closure and reduction exists in two geometrically isomeric forms (VIII and VIIIa) whereas that similarly derived from VII exists in one racemic form (IX).



An interesting point to notice is that *cis*-decalin contains 4.6 cal. per mole more energy than the *trans* form—as shown by the heats of combustion. This difference cannot be explained on the basis of Mohr's theory. Differences of this order are to be found between open-chain isomers, such as pentane and isopentane.

⁸⁵ Hückel, *Fortschr. Chem., Physik physik. Chem.*, **19** (4A), 1 (1927).

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CHAPTER 3

THEORY OF THE STRUCTURE AND REACTIONS OF AROMATIC COMPOUNDS

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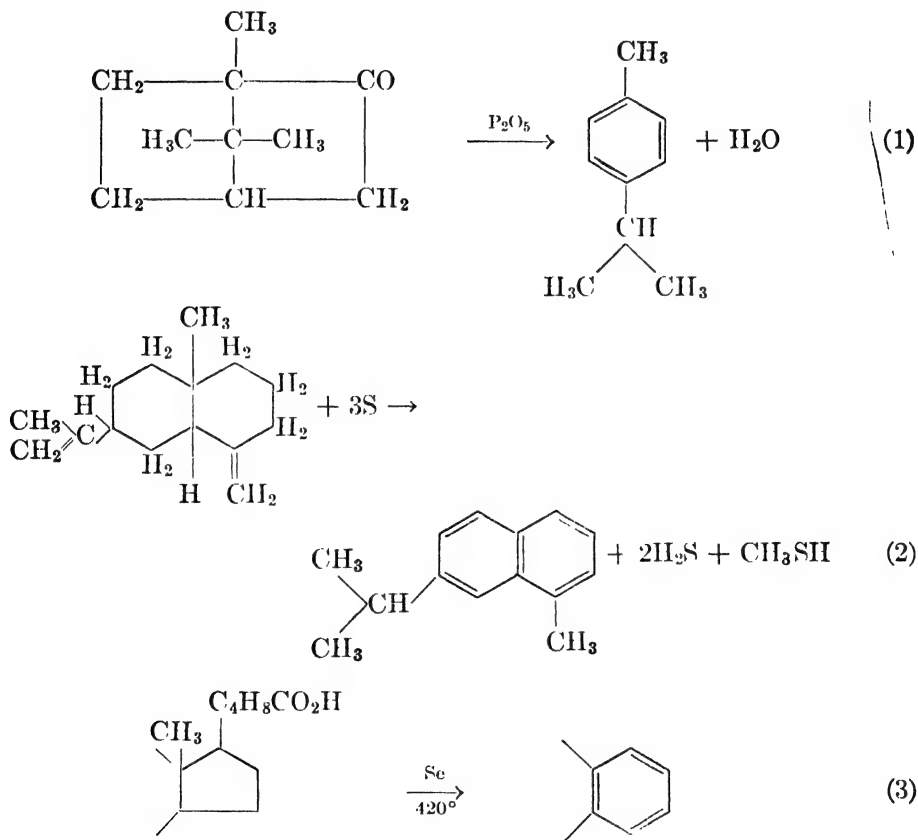
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STRUCTURE

Though the formulation of a simple definition of the term "aromatic character" or "aromaticity" presents certain difficulties, it may be said that the most important and distinguishing characteristics of the aromatic compounds are associated with their peculiarly diminished unsaturation and with the pronounced tendency of these substances to the formation and preservation of type. Benzene clearly is an unsaturated hydrocarbon, for under suitable conditions it can be hydrogenated, but the compound is so much less reactive than the simple alkenes and alkynes that the unsaturation appears to be of a special, modified character. The hydrocarbon reacts only slowly with bromine; it fails completely to combine with hydrogen bromide; and, although it decolorizes

permanganate in a cold acidic solution sufficiently rapidly for test purposes,¹ the unsaturated hydrocarbon is quite stable to alkaline permanganate in the cold. Hand in hand with this unusual resistance to chemical attack is the general stability of the benzene ring system. The ease of formation and the stability of the unsaturated ring are well illustrated by the production of aromatic compounds in the pyrolysis of coal and in such remarkable transformations as the conversion of camphor into



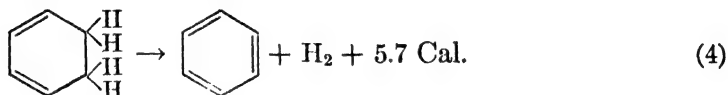
p-cymene (1), or the dehydrogenation of the sesquiterpene α -selinene (2). Other examples are the ring enlargement and aromatization occurring in the dehydrogenation of cholic acid (p. 1351) with selenium at a high temperature (3), and the conversion of *n*-butyl-cyclopentane into *o*-ethyl-toluene on dehydrogenation with palladium charcoal.²

The special stability of the benzenoid nucleus as compared with less highly unsaturated cyclic systems is indicated with striking clarity by thermochemical data. Whereas early measurements of heats of combus-

¹ Wieland, *Ber.*, **45**, 2615 (1912).

² Kasansky and Plate, *Ber.*, **69**, 1862 (1936).

tion³ indicated that the formation of benzene from dihydrobenzene requires an energy input amounting to one-fifth to one-fourth that involved in the removal of two hydrogen atoms from cyclohexane or cyclohexene, it has been shown more recently by the direct determination of heats of hydrogenation that the conversion of 1,2-dihydrobenzene into benzene actually is a slightly exothermic reaction (5.6 Cal.).⁴ It is almost certain that dihydrobenzenes are thermodynamically unstable with respect to benzene and, consequently, that reaction 4 will proceed in the direction indicated under the influence of a suitable catalyst.



Halogen and hydroxyl derivatives of 1,2- and 1,4-dihydrobenzene, such as 1,2-dibromo-1,2-dihydrobenzene, hitherto have eluded isolation, and the lack of stability of these compounds probably is attributable to similar energy relationships.

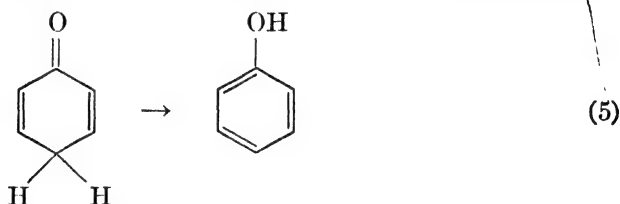
It is a further mark of the aromatic character that the chief reactions of the compounds in question are substitutions rather than additions. The line of demarcation is by no means a sharp one, and examples will be cited below of additions to aromatic compounds as well as of substitutions of alkenes, but the general difference in the reaction type nevertheless is impressive. In defining aromaticity, however, the type of reaction is given a place of secondary importance because it is in all probability a direct consequence of the properties discussed above. A distinct parallelism is easily discernible, for where the ring system is particularly stable and inert, as it is with nitrobenzene or pyridine, only substitution occurs, and that with difficulty; naphthalene and anthracene are more susceptible to any kind of reaction, they are more like alicyclic ethylenic hydrocarbons, and they often yield addition products. It is only where the stability characteristic of the aromatic condition is not highly developed that an addition product of a dihydrobenzenoid structure is capable of existence. It is properly said that nitrobenzene possesses a higher degree of aromaticity than benzene and that naphthalene is less strongly aromatic than the parent hydrocarbon. The greater susceptibility of naphthalene than benzene to addition reactions is a mark of its inferior aromaticity.

That functional groups sometimes display a somewhat unique character further distinguishes the benzenoid compounds. When compari-

³ Stohmann and Langbein, *J. prakt. Chem.*, [2] **48**, 447 (1893); Roth and v. Auwers *Ann.*, **407**, 145 (1915).

⁴ Kistiakowski, Ruhoff, Smith, and Vaughan, *J. Am. Chem. Soc.*, **58**, 146 (1936).

son is made with open-chain compounds which are unsaturated, however, the differences often are slight. The inert nature of the halogen atom in bromobenzene is encountered also in vinyl bromide, and the phenols are comparable in acidic strength to the aliphatic enols. Although the existence of diazonium compounds of the aromatic, but not of the aliphatic, series appears to indicate a unique property of the aromatic amines, it is possible that the discrepancy is due merely to lack of data upon which to base an accurate comparison. One real difference is that the hydroxyl derivatives of benzene show much less tendency to ketonize than do the aliphatic enols, but this is only another manifestation of the special stability of the unsaturated ring or, conversely, of the thermodynamic instability of the dihydride structure of the keto form (5).

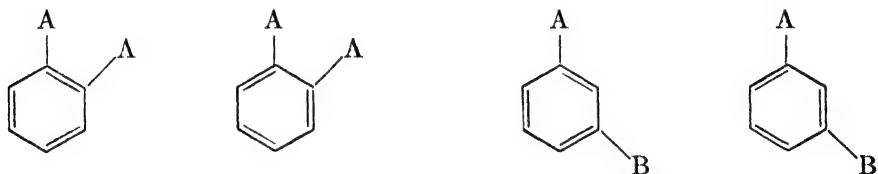


Finally, it may be noted that the benzene ring not only is capable of persisting throughout many transformations of side chains and substituents, but also functions as a closely knit unit in which each part is coordinated with the whole. A substituent not only influences the reactivity at an adjacent carbon atom but also modifies the character of the entire ring, and the transmittance of an orienting or activating effect to the *para* as well as the *ortho* position illustrates clearly the special nature of the aromatic compounds in this respect.

Although the formulation of a theory which will best account for the special characteristics of the aromatic compounds usually is referred to as the benzene problem, benzene is only one representative of a large number of cyclic substances which possess to a greater or less degree the properties listed above, and an adequate theoretical interpretation should be broad enough to include the polynuclear aromatic hydrocarbons and the unsaturated heterocycles of aromatic characteristics. Conversely, the modification in properties produced by fusing together two or more benzene rings, or by the insertion of a hetero atom, may serve to reveal tendencies not directly discernible in the unmodified molecule. In the following inquiry into the problem, an attempt will be made to assemble and evaluate the pertinent facts concerning all the aromatic types.

Benzene Formulas. There is abundant evidence from the facts of isomerism, from hydrogenation experiments, and from crystal-structure

studies that benzene contains a ring of six equivalent carbon atoms, each carrying an atom of hydrogen. The only problem is that of accounting for the fourth valence of each carbon atom. Of the many solutions which have been suggested, only two can be said to make use of the ordinary conception of the valence bond, namely, the formulas of Kekulé (1865) and of Ladenburg (1869).^{*} The formulation which originally was given preference by Kekulé, largely because of its simplicity, has been the subject of continued experimental investigation and debate, and there is much to recommend the conception of a ring system of alternate double and single bonds. For a preliminary examination of the various hypotheses it will be sufficient to show why many of Kekulé's contemporaries were led to consider his formula inadequate and to construct alternate hypotheses. One much-discussed objection was raised by Ladenburg,⁵ who pointed out that although the Kekulé formula predicts the existence of only one monosubstitution product of benzene and is thus in accordance with the known facts, it allows the existence of a greater number of disubstitution products than are actually known. Among such derivatives there should be two *ortho* compounds and, when the two groups are different, two *meta* compounds. These predictions were contrary to



all experience. In many cases disubstitution products of the types indicated had been prepared by methods which utilized a different sequence in the introduction of the groups and only a single *ortho* or *meta* derivative was obtained.

In reply to Ladenburg's criticism, Victor Meyer⁶ offered the reasonable opinion that the distinction between the two possible isomers probably is so subtle as to escape detection by ordinary methods. Kekulé,⁷ however, felt that Meyer's stand was too weak, and he constructed a mechanistic picture, the essence of which is that the double bonds are assumed to be in a constant state of oscillation between the

^{*} References to the early literature may be found in Beilstein-Prager-Jacobson, "Handbuch d. org. Chemie," 4th ed., Springer, Berlin (1922), Vol. V, pp. 173-174; good discussions are given in Cohen, "Organic Chemistry," 5th ed., Longmans, Green and Co., London (1928), Part II, pp. 422-468, and in Meyer-Jacobson, "Lehrbuch d. org. Chemie," Veit & Comp., Leipzig (1902), Vol. II, Part I, pp. 46-7^c

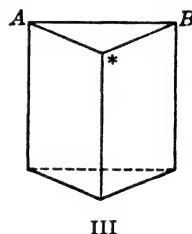
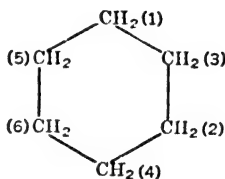
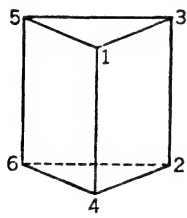
⁵ Ladenburg, *Ber.*, **2**, 140 (1869).

⁶ Meyer, *Ann.*, **156**, 293 (1870).

⁷ Kekulé, *Ann.*, **162**, 85 (1872).

two possible positions. This idea was open to the criticism that, regarded as a proposal of dynamic isomerism, it did not correspond with the discovery that the interchange between actual tautomers often occurs with measurable velocity. It is not so inconsistent with the modern concept of resonance (p. 1950), but in its time, the oscillation hypothesis only served to divert attention from the views based upon sound analogy and to weaken the standing of the double-bond formula.

A further, rather serious objection to the Kekulé formula arose from the difficulty of understanding why, if benzene contains three ordinary double bonds, it is so inferior to the ethylenic hydrocarbons in reactivity. Most of the later formulations were designed to express in some way the modified unsaturation peculiar to the aromatic compounds. The extreme attempt in this direction is the Ladenburg prismatic formula, which may be said to indicate no unsaturation at all, in the ordinary sense, and thus to represent a very inert and stable molecule. In the accompanying formula (I), a carbon and hydrogen atom are assumed to occupy each



corner of the figure, and the positions are numbered so as to correspond to those of the more familiar hexagonal formulas. In order to conform to the Körner principle of orientation the 1,2-, 1,3-, and 1,4-positions must be regarded as *ortho*, *meta*, and *para*, respectively. Thus a 1,4-derivative (*para*) would be the only isomer capable of giving rise to but a single monosubstitution product.

The Ladenburg formula actually is of only historical interest, for it is disproved quite definitely by a number of observations. Some mention of the evidence may be not out of place, however, for this will at least show certain of the requirements which a formula must meet in order to be admissible. In point of time the first demonstration of the inadequacy of the prism formula was that adduced by Baeyer in his classical researches on the hydrophthalic acids, commencing in 1886. The prismatic form of benzene pictured by Ladenburg would have to open on hydrogenation in such a way, for example, that the 1 and 3, or *meta*, positions would be adjacent to each other in the resulting cyclohexane, as pictured in formula II. Baeyer, however, developed a thorough experimental proof that substituents in the hydrogenation products

are not found in the positions indicated but rather that groups attached in the *ortho* positions in benzene are located on adjacent carbons in the cyclohexane formed.* Further objections to the prism formula are that it is incapable of accounting for the polynuclear hydrocarbons and that it does not meet the requirements of space symmetry. The introduction of two different groups, as in formula III, would give rise to molecular asymmetry (p. 221), but no such simple benzene derivative has been found capable of resolution, and there is no instance of an optically active natural product which owes its activity to the asymmetry of an isolated benzene nucleus.

Perhaps the most convincing evidence is that furnished by the recent x-ray crystallographic studies. Investigations in this field (p. 1762) have shown that all six carbon atoms of benzene lie in a plane and that the hydrogen atoms or substituent groups radiate from the ring in the same plane. It is possible that the ring is slightly puckered, but any such deformation must be practically inappreciable, and it certainly does not represent a permanent condition.⁸ From the x-ray analysis of hexamethylbenzene, and with the aid of certain inferences by Bragg⁹ regarding naphthalene and anthracene, Lonsdale¹⁰ determined the distance between carbon centers in the aromatic ring and estimated other dimensions of the hexamethylbenzene molecule. The results for this and other aromatic compounds obtained by various investigators¹¹ are in substantial agreement with those of Lonsdale, and the conclusions based upon x-ray measurements have been confirmed and extended by application of the electron diffraction method. The dimensions for the benzene molecule given in the accompanying figure are those reported by Jones.¹² The length of the aromatic carbon-carbon bond (1.40 Å) is known with an accuracy of ± 0.01 Å, while the value for the C_{aromatic}—H bond (1.14 Å) is subject to somewhat greater uncertainty. The establishment of the planar nature of the benzene ring definitely excludes the prism structure proposed by Ladenburg as well as several other three-dimensional representations which have been suggested. These space formulas have been reviewed and criticized by Graebe¹³ and by Wittig,¹⁴ and they need not be discussed here.

* For reviews of this work see: Cohen, *loc. cit.*, pp. 440–449; Meyer-Jacobson, *loc. cit.*, pp. 764–771.

⁸ Bergmann and Mark, *Ber.*, **62**, 750 (1929).

⁹ Bragg, *Proc. Phys. Soc. (London)*, **34**, 33 (1922); **35**, 167 (1923).

¹⁰ Lonsdale, *Trans. Faraday Soc.*, **25**, 352 (1929).

¹¹ Robertson, *Chem. Rev.*, **16**, 434 (1935).

¹² Jones, *Trans. Faraday Soc.*, **31**, 1036 (1935).

¹³ Graebe, *Ber.*, **35**, 526 (1902).

¹⁴ Wittig, "Stereochemie," Akademische Verlagsgesellschaft, Leipzig (1936), pp. 157–160.

The experimentally determined distance separating adjacent carbon centers in the benzene ring is 1.40 \AA , and this may be said to represent the length of the ordinary *ortho* bond. It will be seen from the figure that a valence linkage between *para* carbon atoms would constitute a bond twice this length (2.80 \AA). This value is considerably greater than the distance between carbon centers in any known type of compound,

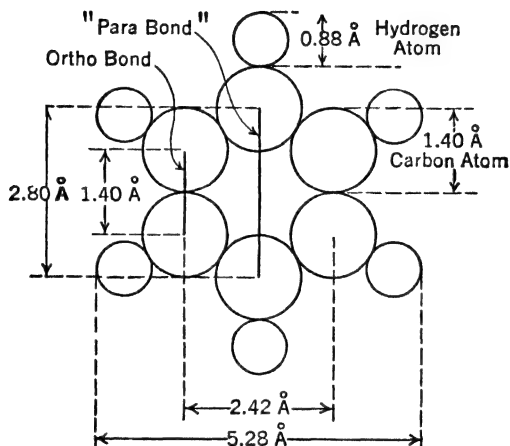


FIG. 1

as can be seen from a comparison with the results obtained for various kinds of linkages:^{11, 12} C—C bond in diamond, 1.54 \AA ; C—C bond in graphite, 1.42 \AA ; C_{aliphatic}—C_{aliphatic} bond in normal alkanes, 1.54 \AA ; C_{aromatic}—C_{aliphatic} bond in alkyl benzenes, $1.47\text{--}1.50 \text{ \AA}$; C=C bond in benzoquinone, 1.32 \AA . It is evident that an aromatic *para* bond would represent something quite unlike any known type of linkage, and consequently that all formulas for benzene which employ such a bond must be considered as being of a purely speculative nature. While it is possible that an adequate solution of the benzene problem can be found only with the aid of some special hypothesis with regard to valence, it is well to differentiate clearly between those theoretical concepts which are based upon analogies with known compounds and those which postulate a type of linkage not encountered among non-benzenoid compounds, and formulas utilizing the idea of a *para* bond clearly belong to the second, speculative, group.

One of the earliest of the suggestions utilizing the *para* bond is the diagonal formula of Claus. The idea of a direct connection to both the *ortho* and *para* positions was considered to be of great advantage in providing a mechanism whereby a substituent can exert an influence in both these positions, and the hypothesis was particularly attractive

during the years when little or nothing was known concerning the nature of conjugated systems and 1,4-additions, and hence when it was not yet possible to understand the close relationship of the *para* carbon atoms on the basis of the Kekulé formula. Even with these modern developments, the Claus formula has continued to receive occasional attention, as for example in the electronic interpretation of the diagonal formula proposed by Pauling.¹⁵ That the Claus formula assumes a con-



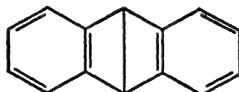
Claus, 1867

figuration for the carbon atom which departs widely from the normal is perhaps an insufficient reason for its rejection. That it calls for three valence bonds of twice the ordinary length, and that it requires the assumption that these special bonds confer upon the molecule a remarkable degree of stability, classifies the hypothesis as being not only speculative but improbable. Since aliphatic carbon-carbon bonds are slightly longer and slightly weaker than the aromatic linkage between *ortho* carbon atoms, it may be inferred that a long bond connecting *para* carbon atoms in the benzene ring would represent a very weak linkage. The diagonal formula, therefore, would imply an extremely reactive molecule quite different in properties from benzene. Pauling¹⁶ subsequently called attention to this defect in the hypothesis which previously he had supported. The chemical evidence is of a negative character, but it points in the same direction. By partial hydrogenation (Baeyer) or by ring cleavage (Th. Zincke) one of the unsaturated linkages can be opened under conditions not likely to affect the remaining centers of unsaturation. The latter appear in the reaction products not as *para* bonds but as ordinary double linkages. Examples of such reactions will be given later.

The theoretical objections to a *para* bond of any sort apply equally well to the structure suggested by Dewar and utilized in Graebe's anthra-



Dewar, 1867



Graebe, 1867

cene formula. There is some justification for representing the *meso* carbon atoms of anthracene as being connected by a long, weak bond in order to account for the great reactivity at these positions, and the

¹⁵ Pauling, *J. Am. Chem. Soc.*, **48**, 1132 (1926).

¹⁶ Pauling and Wheland, *J. Chem. Phys.*, **1**, 362 (1933).

Graebe formula will be given further consideration in a later section. As applied to benzene, the formulation received little attention until revived by Ingold¹⁷ in 1922 in order to account for the transmission of a directive influence to the *para* position. Some secondary hypothesis is required to provide for the known symmetry of benzene, and Ingold considered the Dewar formula to be an intermediate phase of oscillation between the two Kekulé structures. It would, however, represent far too reactive a structure to have a finite existence in the chemical sense, for activity would arise not only from the *para* bond but also, as remarked by R. Robinson,¹⁸ from the two isolated ethylenic linkages.

The Armstrong-Baeyer centric theory¹⁹ represents a speculation of still another kind. The fourth valence of each carbon atom is not considered to be connected to any other atom but is pictured as being directed toward the center of the nucleus. It is supposed that the par-



Armstrong-Baeyer, 1887

tial valences effect a neutralization of energy at the center, that by their mutual action the combining power of each is rendered latent. The centric formula has had a certain appeal because it gives formal expression to the fact that the benzene ring possesses certain peculiarities, but one might argue that the same purpose would be served by the use of a plain hexagon labeled "Ar." The hypothesis of stabilizing partial valences in no way solves the mystery of the stability of the ring; it simply states the problem in a different way. The lines directed toward the center are not intended to represent free valences, and it is difficult to assign to them any real physical meaning except, perhaps, that the formula may be taken to indicate a cluster of six electrons at the center of the carbon ring. This and other electronic conceptions will be discussed below. For the present it may be noted that, since the centric formula is beyond the reach of experimental evaluation, its only claim to merit would have to be derived from a demonstration of its usefulness in the correlation of facts. Bamberger²⁰ attempted such a correlation in the field of those unsaturated heterocycles which possess to a greater or less extent the properties characteristic of the aromatic condition. His representations of a few of these substances are shown in the formu-

¹⁷ Ingold, *J. Chem. Soc.*, **121**, 1133 (1922).

¹⁸ Robinson, *Ann. Repts. Chem. Soc. (London)*, **29**, 86 (1922).

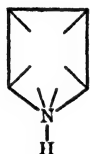
¹⁹ Armstrong, *J. Chem. Soc.*, **51**, 264 (1887); Baeyer, *Ann.*, **245**, 121 (1888); **251**, 285 (1889); **269**, 188 (1892).

²⁰ Bamberger, *Ber.*, **24**, 1758 (1891); *Ann.*, **273**, 373 (1893).

las. The formula for pyridine resembles closely that for benzene, and the trivalency of nitrogen is in accord with the fact that pyridine forms stable salts and alkyl halide addition products. In pyrrole, however, the nitrogen atom is assumed to be pentavalent, and the fact that this heterocycle does not form stable salts is laid to the utilization of the salt-forming valences of nitrogen in contributing to the centric system of the ring. In the same way, thiophene and furan are regarded as containing tetravalent hetero atoms, and indeed the former compound does



Pyridine



Pyrrole



Thiophene



Pyrazole



Furan

not add alkyl halides. According to Bamberger, all these heterocycles resemble benzene in having six valences directed toward the center, and he took it as axiomatic that the aromatic character is in each case due to the hexacentric system.

This view, though interesting and suggestive, is open to certain objections. In a paper of 1894, Knorr²¹ criticized Bamberger's formulas for pyrrole and pyrazole on the ground that open-chain compounds having only alkyl groups or hydrogen atoms joined to pentavalent nitrogen, analogous to the hypothetical structures, were entirely unknown. The hypothesis becomes no more reasonable now that such compounds have been discovered, for they are highly unstable substances entirely different from pyrrole, and the fifth alkyl group is held by a valence which is very closely akin to a polar bond (p. 1837). It may be argued further that some of the alkylated pyrroles do appear capable of salt formation, while retaining the aromatic properties. It is also worth noting that the weak basicity of pyrrole can be explained just as well by means of the double bond formula (IV). On this basis, the heterocycle is comparable with an imide (V) or with diphenylamine (VI), and the lack of strong salt-forming qualities is attributable to the presence of unsaturated substituents joined to nitrogen²² (see p. 210).

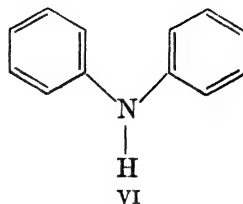
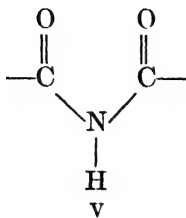
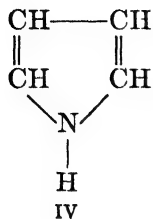
Like Armstrong and Baeyer, Thiele²³ sought to account for the diminished unsaturation of benzene by the use of a novel conception of the nature of valence. Starting with the Kekulé formula, and with the idea that

²¹ Knorr, *Ann.*, **279**, 188 (1894).

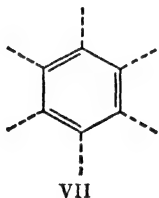
²² Marckwald, *Ann.*, **279**, 1 (1894).

²³ Thiele, *Ann.*, **306**, 125 (1899).

a partial valence is associated with every unsaturated atom, Thiele supposed that the six partial valences of benzene, VII, neutralize each other



in pairs to form three inactive double bonds, as in VIII. The original double bonds are thereby rendered inactive as well, and the distinction between these bonds and the newly formed linkages may be so slight that the final result is perhaps best represented as in IX. Any difference

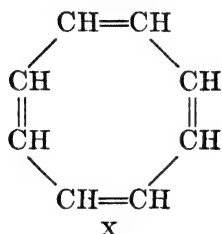


Thiele, 1899

between *ortho* positions vanishes, and benzene is represented as a symmetrical ring of six inactive, semi-double bonds which are regarded as conferring upon it a special stability. Thiele's second formula amounts to practically the same thing as the centric formula, for in each case there is pictured an internal neutralization of the fourth valences of the ring atoms. There is the difference, however, that, although Thiele did not provide a theoretical mechanism whereby the supposed neutralization or dampening might take place, and although the partial valences cannot be said to possess a physical reality, Thiele did develop a conception of the reason for the inertness of the benzene ring based upon a rational comparison with open-chain compounds. It is quite generally true that a conjugated system is more stable and more prone to function as a unit than a system of the same degree of unsaturation but lacking the feature of conjugation. According to the Kekulé formula, benzene contains a particularly symmetrical, closed conjugated system of double and single linkages, and this feature may well confer upon the molecule a special stability. It is difficult to see any great advantage in the attempt to express this idea by means of a special formula such as VIII, for the curved lines have no significance in terms of the modern conception of the nature of the chemical bond. The simple Kekulé formula,

interpreted as indicating a special type of conjugation, serves just as well, and the contribution of Thiele to the general problem was in concentrating attention on this interpretation.

Although this structural feature is doubtless of considerable importance, it appears that the idea of conjugation alone does not solve the problem. If the aromatic character of benzene were attributable solely to a symmetrical, cyclic system of alternate double and single bonds, cycloöctatetraene (X) might be expected to possess the same inert, stable character as benzene. Willstätter²⁴ prepared a hydrocarbon



presumably having this structure and found that the substance is yellow, decolorizes permanganate instantly, forms a dibromide and a hydrogen bromide addition product, and rearranges easily when in a slightly impure condition to a more stable product, possibly having a bridged structure. Hurd and Drake²⁵ have noted that no proof was provided that the Willstätter hydrocarbon has a conjugated system, and they have expressed the view that the substance conceivably may have contained an allenic group. Goldwasser and Taylor,²⁶ finding that cyclooctene on catalytic dehydrogenation at temperatures above 400° gives styrene, suggested that the supposed cycloöctatetraene may have been styrene, but in view of Willstätter's identification of cyclooctane as the product of the catalytic hydrogenation of the unsaturated hydrocarbon this conjecture hardly seems admissible. Confirmation of the structure and properties of the hydrocarbon, to be sure, is highly desirable. Attempts to synthesize benzo and dibenzo derivatives of cycloöctatetraene have been initiated.²⁷ If Willstätter's observations regarding cycloöctatetraene are sustained, the properties of the hydrocarbon perhaps constitute a serious objection to the Kekulé cyclohexatriene formula for benzene. It is possible, however, that the real anomaly may be in the nature of cycloöctatetraene rather than benzene (see p. 213). In comparison with certain open-chain conjugated polyenes whose proper-

²⁴ Willstätter and Waser, *Ber.*, **44**, 3423 (1911); Willstätter and Heidelberg, *Ber.* **46**, 517 (1913).

²⁵ Hurd and Drake, *J. Am. Chem. Soc.*, **61**, 1943 (1939).

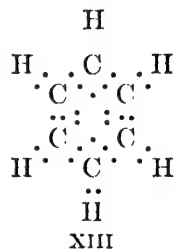
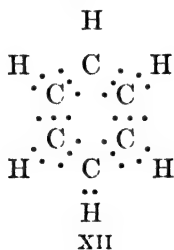
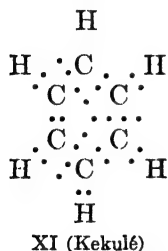
²⁶ Goldwasser and Taylor, *ibid.*, **61**, 1260 (1939).

²⁷ Wawzonek, *ibid.*, **62**, 745 (1940); Fry and Fieser, *ibid.*, **62**, 3489 (1940).

ties will be discussed in a later section, Willstätter's cyclooctatetraene appears to be more reactive and less stable than would be expected, and the compound may not provide a sound basis for the evaluation of the Kekulé formula.

Attempts to synthesize cyclobutadiene thus far have resulted in failure, but from the nature and outcome of the attempts it appears likely that if the hydrocarbon is capable of existence it is a highly reactive and unstable compound wholly unlike benzene. A comparison of the conjugated four- and six-membered unsaturated structures is hardly appropriate, however, for the cyclobutadiene ring could be formed only with considerable departure from the normal tetrahedral angles and would surely be under significant strain. The element of strain probably does not arise with either benzene or cyclooctatetraene.

It is appropriate to conclude this discussion of formulas and theoretical interpretations with an account of the electronic formulations (p. 1970) of benzene, for these give a more concrete expression to the older representations and help to clarify the problem. In the electronic representation of the Kekulé formula (XI), the carbon atoms are connected alternately by a pair of shared electrons, and by two such pairs.



The only essentially different formulation (other than the resonance concept discussed on p. 207) is that first suggested by Kauffmann²⁸ and written by Kermack and R. Robinson²⁹ as shown in formula XII, the electrons connecting the nuclear carbon atoms being distributed evenly in triplets. The formula can be written in various ways without altering the essential idea which it is intended to convey. The six electrons not required for the single binding of the carbon atoms may be regarded as forming a stable association having an unspecified location in the center of the ring,³⁰ for example, or the formula may be written as in XIII. The sextet of central electrons is supposed to confer upon the molecule its special aromatic character. Goss and Ingold³¹ pointed out that the aromatic heterocyclic compounds can be correlated with benzene by

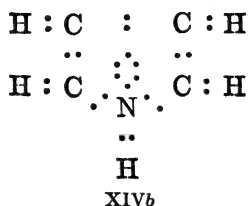
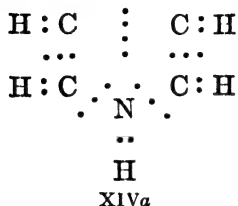
²⁸ Kauffmann, "Die Valenzlehre," Enke, Stuttgart (1911), p. 539.

²⁹ Kermack and Robinson, *J. Chem. Soc.*, **121**, 427(1922).

³⁰ Armit and Robinson, *ibid.*, **127**, 1604 (1925).

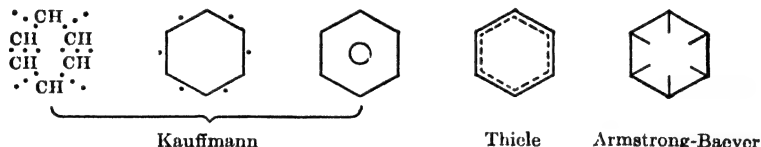
³¹ Goss and Ingold, *ibid.*, 1268 (1928).

adopting Bamberger's hypothesis regarding the valence of the nitrogen atom in the five-membered rings. Pyrrole, for example, can be assigned the formula *XIVa* or *XIVb*, the latter giving particular prominence to the aromatic sextet. Bamberger's "rule of six" thus finds an exact



electronic counterpart, but the latter is no more accurate as an empirical classification than the former, and atomic-structure theory offers no explanation for the supposed rule that the sextet of electrons is responsible for the stability of the aromatic nucleus.

The electronic formulas XII and XIII, originating in the suggestion of Kauffmann, may be represented in various simplified forms, as indicated. A little reflection will show that the essential idea which any of the formulas is intended to express is exactly the same as that given by

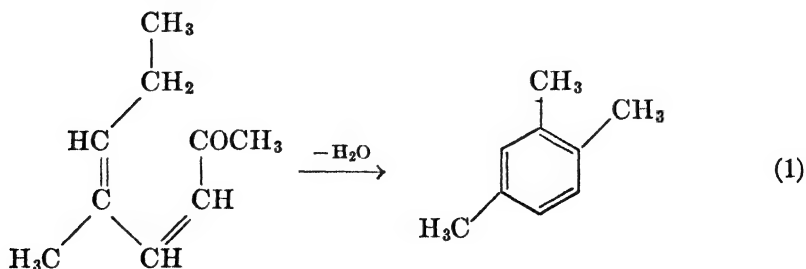


Thiele's second formula, namely, that there is no distinction between any of the six bonds in the ring and that these are all of a different character from any known type. It is likewise evident that if the centric formula of Armstrong and Baeyer can be given any interpretation in terms of the modern conception of valence it must take the form of this same Kauffmann structure, which for this purpose might be written as in formula XIII, above. All the formulas under discussion are really equivalent, and the idea which they represent, and which may be said to be embodied in the hypothesis of a centric-electron structure, is that all six carbon-carbon linkages are identical. This view in no sense explains the stability of the aromatic ring, but it suggests that this is in some way dependent upon a central electron-smear containing just six electrons. The suggestion is necessarily vague, for it is difficult to see how the static formula can be translated in terms of a dynamic, orbital structure. The position of the heterocycles in this scheme also must be regarded as highly speculative. The fundamental assumption of complete symmetry, however, represents a perfectly definite point of view and one which is perhaps capable of being tested.

Of the other formulas which have been discussed, that of Ladenburg is quite definitely excluded, and the formulas of Claus and of Dewar are so highly improbable that they also may be ruled out. The only alternative to the above view is that represented by the Kekulé formula, and it matters little whether this is written with bonds or with electrons, or whether Thiele's curved lines of neutralization are included, so long as these are given no physical meaning and understood merely to draw attention to the conjugation.

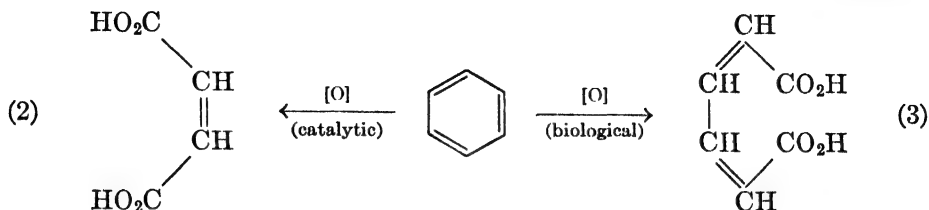
Here, then, are two quite definite views regarding the constitution of the aromatic compounds. The one postulates the presence in benzene of three double bonds; the other holds that there are no such linkages. According to one formulation the two *ortho* positions may be different, and according to the other they are quite indistinguishable. Out of the enormous accumulation of facts regarding the reactions of the aromatic compounds there should be evidence sufficient to distinguish between the two possibilities, and in the following pages an effort will be made to evaluate the pertinent material. It also may be possible to show that one formula or the other offers a better explanation of certain facts and hence is the more likely to be true. Since the Kekulé formula alone can be compared with known types, it must bear the entire burden of the proof, with respect to both the direct and the circumstantial evidence, and the following survey will consist largely of an inquiry into the validity and the usefulness of the Kekulé formula.

The Question of the Presence of Double Bonds. Evidence derived from reactions of synthesis and of degradation lacks conviction because of the possibility that the double bonds known to be present in the starting materials, or found in the degradation products, disappear with the formation of the ring, or appear with its rupture. It may be said only that the Kekulé formula offers a ready and satisfactory interpretation of such reactions. Examples of syntheses which would be expected to yield cyclohexatriene derivatives are found in the polymerization of acetylene at 500° to benzene, the formation of mesitylene from acetone, and Barbier and Bouveault's ³² synthesis of pseudocumene (1). As ex-

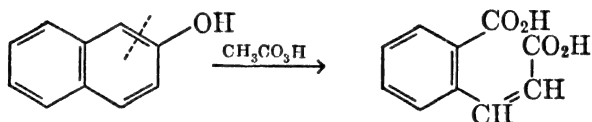


³² Barbier and Bouveault, *Compt. rend.*, **120**, 1420 (1895).

amples of degradations which seem to reveal the presence of double bonds in the aromatic nucleus, mention may be made of the oxidation of benzene by catalytic methods to maleic acid (2), and of the oxidation



of the hydrocarbon in the organism of the dog to muconic acid³³ (3). Another reaction which appears to follow the course ordinary for unsaturated compounds is the oxidation of β -naphthol with permanganate³⁴ or with peracetic acid (yield, 73 per cent)³⁵ to *o*-carboxycinnamic acid (4).



More secure evidence for the presence of double bonds in aromatic rings is furnished by the isolation of certain products of addition. Addition products are encountered much less frequently with benzene than with the polynuclear hydrocarbons, but a few definite examples of such substances are known. Although benzene is somewhat more resistant to hydrogenation than open-chain unsaturated compounds, the absorption of three moles of hydrogen proceeds smoothly when a suitable catalyst is used and all traces of thiophene are eliminated from the hydrocarbon. Benzene also is capable of adding three moles of chlorine or of bromine without liberation of hydrogen halide. The reactions proceed rapidly under the accelerating influence of light and in the absence of oxygen, which has a pronounced anticatalytic effect.³⁶ The reaction with ozone is particularly convincing, for with ordinary compounds the formation and degradation of an ozonide is taken as excellent evidence of the presence of a pair of unsaturated carbon atoms. The reaction of benzene with ozone does not proceed very smoothly, but there is formed a triozone which undergoes decomposition in the usual way to give glyoxal.³⁷ An addition involving only one of the three centers of unsaturation has been observed in only a single instance.

³³ Jaffé, *Z. physiol. Chem.*, **62**, 58 (1909).

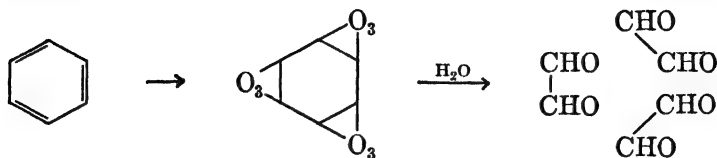
³⁴ Ehrlich and Benedikt, *Monatsh.*, **9**, 527 (1888).

³⁵ Böeseken and von Königfeldt, *Rec. trav. chim.*, **54**, 313 (1935).

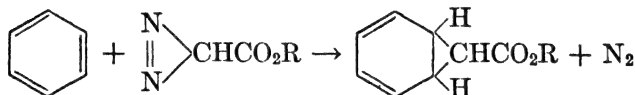
³⁶ Luther and Goldberg, *Z. physik. Chem.*, **56**, 43 (1906).

³⁷ Harries and Weiss, *Ber.*, **37**, 3431 (1904); Harries, *Ann.*, **343**, 311 (1905).

Buchner³⁸ found that diazoacetic ester reacts with benzene at 150° with loss of nitrogen and addition of the acetic ester residue to adjacent posi-



tions in the ring. The formation of a norcaradiene carboxylic acid ester is entirely analogous to the production of cyclopropane esters from



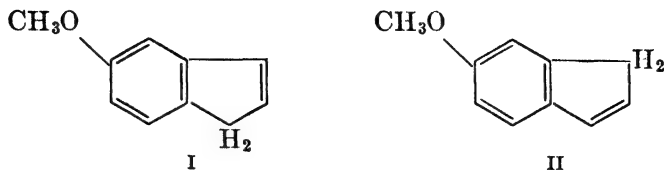
aliphatic ethylenic compounds. Similar products were obtained from toluene and the three xylenes, while with mesitylene the cyclopropane derivative, if formed, is isomerized at once to a cycloheptatriene derivative.

Though it is possible with the aid of suitable assumptions to account for these reactions on the basis of the centric electron formula, the simplest explanation of the formation of addition products in the reaction of benzene with ethylenic reagents is that ethylenic bonds are present in the molecule. Consequently, it is a matter of importance to consider more fully the possible location of these bonds in some of the substitution products of benzene.

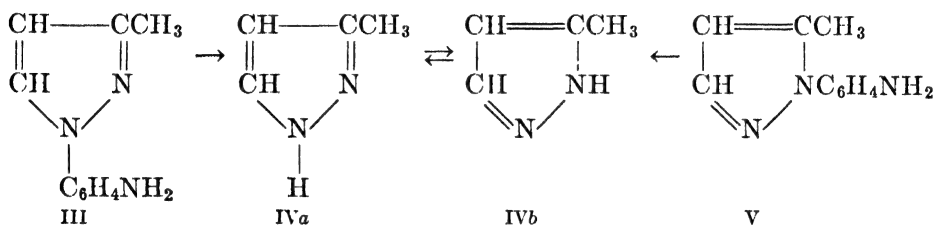
The Question of Isomeric Kekulé Forms. The fact that isomeric *ortho* compounds have not been discovered is a far less valid objection to the Kekulé formula today than when Ladenburg originally raised the question. A similar argument was once cited against the Sachse-Mohr non-planar formula for cyclohexane, and for many years the formula was rejected largely because it predicted two isomers where none were found. Isomeric forms of cyclohexane itself are still unknown, and yet on the basis of other evidence the Sachse-Mohr theory (p. 69) has been firmly grounded. There is reason to believe that more than one form of cyclohexane can exist, but that the difference between the forms is very slight and that the transformation of one form to another can be accomplished with very little expenditure of energy. This is no true analogy to the case of benzene, but rather an interesting historical parallel. There are, however, some analogies for the interconversion of possible isomers by

³⁸ Buchner and Curtius, *Ber.*, **18**, 2377 (1885); Buchner, *Ber.*, **29**, 106 (1896); Buchner and Delbrück, *Ann.*, **358**, 1 (1908); Buchner and Schulze, *Ann.*, **377**, 259 (1910); Buchner and Schottenhammer, *Ber.*, **53**, 865 (1920).

the shifting of double bonds. Methods calculated to yield the methoxy-indenes I and II have been found to give a single compound.³⁹ Another



example is from the field of the heterocyclic compounds. Knorr²¹ found that each of the isomeric pyrazole derivatives, III and V, can be converted by oxidation of the substituted N-phenyl group, and decarboxylation, into a methylpyrazole. The same product was obtained in each



case, and consequently it is seen that the structures IVa and IVb probably represent mobile tautomers. This methylpyrazole, it may be noted, is in every sense an aromatic compound, for it can be nitrated or sulfonated, and on oxidation the methyl group is attacked rather than the ring.

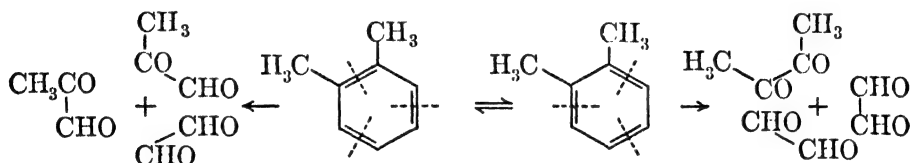
Pairs of isomers no more exist in these instances than with ordinary *ortho* derivatives of benzene, and this is true even though the interconversion involves, in addition to a shifting of double bonds around a symmetrical ring, the migration of a hydrogen atom. The view of Victor Meyer that the difference between the *ortho* isomers would be so slight as easily to escape detection appears to be altogether rational. Graebe¹³ took much the same view, but added the further suggestion that for each *ortho* compound one of the Kekulé structures may be slightly more stable than the other, and that the conversion to this more stable form probably takes place with great ease. Reddelien⁴⁰ further remarked that the *ortho* isomers should be regarded as tautomeric, and he expressed the view that the introduction of heavy groups might stabilize one tautomeric form to the extent that this might be detectable, possibly by some delicate diagnostic reaction. He suggested the use of ozone, and it is interesting to note that this reagent has indeed been found

³⁹ Ingold and Piggott, *J. Chem. Soc.*, **123**, 1469 (1923).

⁴⁰ Reddelien, *J. prakt. Chem.*, [2] **91**, 213 (1915).

to serve the purpose. Levine and Cole⁴¹ obtained three products from the ozonization of *o*-xylene, namely, glyoxal, methylglyoxal, and diacetyl. Neither form of the xylene could yield all three oxidation products, and hence it was concluded that the hydrocarbon consists of an equilibrium mixture of the two Kekulé forms. This important observation has been repeated and fully confirmed by Wibaut and Haayman,⁴² who isolated the three carbonyl compounds as the oximes in total yield of 20 per cent and in the ratio calculated for a mixture of equal parts of the two Kekulé forms.

Mills and Nixon⁴³ were led to suspect that the attachment of an alicyclic five-membered ring may result in a stabilization of one of the Kekulé forms, or a fixation of the bond structure in the benzenoid nu-



cleus. According to the van't Hoff model, the free bonds in the system $>C=C<$ of an aliphatic compound lie in a plane, and the angle α between each pair of single bonds is the same as that between the carbon valences of methane (109.5°). The angle β which the single bonds make with the plane of the double bond is then $\frac{1}{2}(360^\circ - 109.5^\circ) = 125.25^\circ$ (see Fig. 2a). The angles β and γ are in this case identical and they are

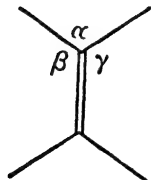


FIG. 2a

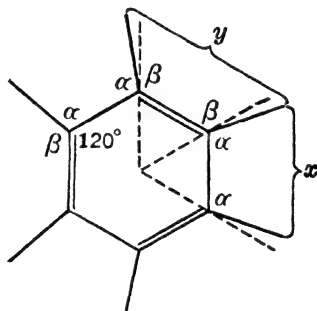


FIG. 2b

considerably greater than the angle α . When the double bond becomes incorporated into a Kekulé ring (Fig. 2b) the situation is altered slightly, for the internal angle γ is reduced from 125.25° to 120° to accommodate ring formation and $\alpha + \beta$ consequently is increased by 5.25° . Whether this

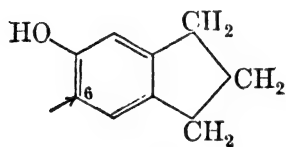
⁴¹ Levine and Cole, *J. Am. Chem. Soc.*, **54**, 338 (1932).

⁴² Wibaut and Haayman, *Nature*, **144**, 290 (1939); *Science*, **94**, 49 (1941).

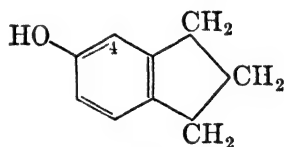
⁴³ Mills and Nixon, *J. Chem. Soc.*, 2510 (1930).

increment is considered to increase one or the other external angle, or to be distributed proportionately between them, β will remain appreciably larger than α . The conclusion is reached that the external valences in the Kekulé ring are not directed toward the center of the hexagon but are inclined at a greater angle from the double bonds of the ring than from the single bonds. Mills and Nixon reasoned further that a five-membered ring can be fused to the Kekulé structure with little distortion of the normal tetrahedral angles if it is attached to *ortho* carbon atoms joined by a single bond (position x , Fig. 2b), for two of the smaller α angles are then incorporated in the new ring. If, however, the attachment were made to doubly bound carbon atoms (y), the new ring including the β angles would be under considerable strain. In consequence of these relationships, the Kekulé form of hydrindene in which the carbon atoms common to the two rings are joined by a single bond should be more free from strain, or more stable, than the alternate form in which there is a double linkage between the rings.

As a means of testing this prediction of the stereochemical theory, Mills and Nixon investigated the diazo coupling and the bromination of 5-hydroxyhydrindene, the two Kekulé forms of which are shown in formulas VIa and VIb. The coupling reaction of phenols is closely related to the coupling of aliphatic enols with diazotized amines, and it is reasonable to suppose that in each case the reaction involves an enolic double bond, $-\text{C}(\text{OH})=\text{CH}-$. Similarly, the ready brominations of phenols and enols appear to be related phenomena and the processes very probably take place by analogous mechanisms. Without making



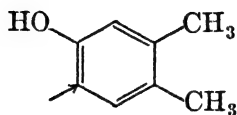
VIa



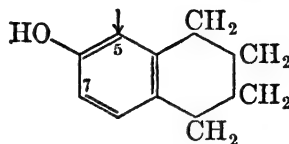
VIb

any specific assumptions regarding the manner in which the enolic double bond participates in these reactions, it can be inferred that the *ortho* coupling and *ortho* bromination of phenols involve substitution at the carbon atom connected to that carrying the hydroxyl group by a double linkage, rather than at the alternate *ortho* position. If the bonds of 5-hydroxyhydrindene are fixed in the positions shown in VIa, coupling and bromination should occur at the enolic *ortho* position 6, while the alternate form of the compound, VIb, should be substituted at position 4. Mills and Nixon found that the substance is attacked very largely in the 6-position (arrow), and this seemed to bear out the theoretical deductions. The observation, however, loses some of its significance

because of the fact that *as-o*-xylenol (VII) yields similar substitution products, for this might mean that the chemical effect of the alicyclic ring is sufficient, without assistance from a steric factor, to direct substitution largely into one of the two available *ortho* positions. On the



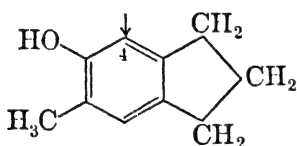
VII



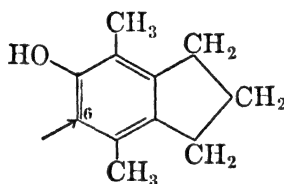
VIII

other hand, the contrasting behavior of 6-hydroxytetralin (VIII) was considered by Mills and Nixon to support the alternative interpretation.

A preferential reaction at one of two available *ortho* positions may be the result of an only moderate preponderance of one of the tautomeric Kekulé forms, or of a slight difference in reactivity between them, and does not necessarily indicate a rigid fixation of the bond structure. A test calculated to detect any fixation of a major character was applied by Fieser and Lothrop⁴⁴ and, more extensively, by Lothrop.⁴⁵ Diazo coupling tests were made with 5-hydroxy-6-methylhydrindene, IX, in which the 6-position is blocked and only the alternate *ortho* position 4 is available, and of the derivative X in which this situation is reversed.



IX



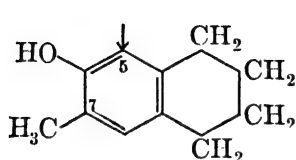
X

Both compounds were found capable of forming azo derivatives, and in a weakly alkaline medium coupling with diazotized *p*-nitroaniline occurs in each case to about the same extent as observed with 2,4-dimethylphenol. The only difference noted between IX and X is that the coupling of the former is inhibited by strong alkali somewhat more effectively than is the coupling of the latter compound, or of β -naphthol. Alkyl derivatives of 6-hydroxytetralin similarly showed no fixation of one or the other bond structure. The introduction of a blocking methyl group at the 7-position (XI) does not interfere with coupling at position 5, and the 5-substituted derivative XII is attacked readily at the free position 7. Lothrop found further that the allyl ethers of the hydroxyhydrindenes IX and X undergo the Claisen rearrangement to *o*-allylphenols without

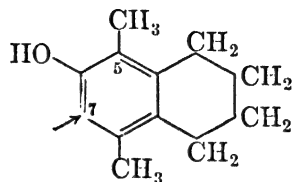
⁴⁴ Fieser and Lothrop, *J. Am. Chem. Soc.*, **58**, 2050 (1936); **59**, 945 (1937).

⁴⁵ Lothrop, *ibid.*, **62**, 132 (1940).

difficulty. Parallel observations were made in the fluorene series.⁴⁶ The results indicate that if any bond fixation exists among hydrindene and tetralin derivatives it can be at most of a qualitative nature and is not comparable with that characteristic of naphthalene (see below).

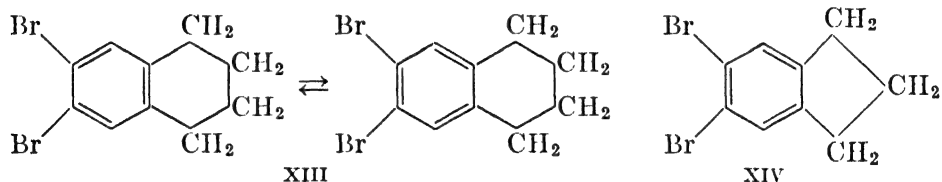


XI



XII

Various observations do indeed indicate that a certain qualitative differentiation exists between the two Kekulé forms of hydrindene, with respect to stability or abundance, and that this is in the direction predicted by Mills and Nixon. Sidgwick and Springall⁴⁷ approached the problem by studying the dipole moments (p. 1752) of suitable *o*-dibromo substituted compounds. The moment of the group Br—C—C—Br in 6,7-dibromotetralin (XIII) was found to be 2.13, and this corresponds exactly with the result obtained for the similarly constituted dibromo-*o*-xylene and agrees well with the value calculated on the assumption that there is no bond fixation (2.12). For the hydrindene derivative



XIV, on the other hand, the observed moment of 1.78 indicates an essential difference in structure and is close to that calculated on the basis of the Mills-Nixon hypothesis that the angle between the *ortho* linkages extending to the bromine atoms is abnormally large. Studies of competition reactions⁴⁸ and of relative reactivities⁴⁹ of hydrindene derivatives point in the same direction. The use of derivatives of the hydrocarbon for the investigation of bond structure introduces some element of uncertainty because of the possibility that the substituent may tend to stabilize one of the Kekulé forms. Long and

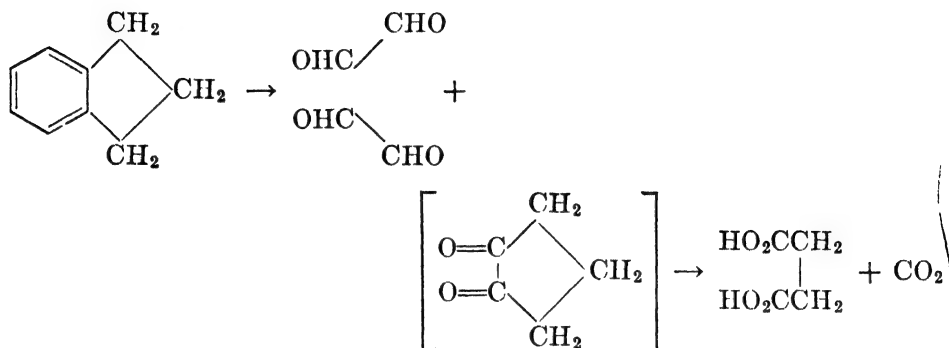
⁴⁶ Lothrop, *ibid.*, **61**, 2115 (1939).

⁴⁷ Sidgwick and Springall, *Chemistry & Industry*, 476 (1936); *J. Chem. Soc.*, 1532 (1936).

⁴⁸ Lindner and co-workers, *Monatsh.*, **72**, 354, 355, 361 (1939).

⁴⁹ Baker, *J. Chem. Soc.*, 476 (1937); McLeish and Campbell, *ibid.*, 1103 (1937); Sandin and Evans, *J. Am. Chem. Soc.*, **61**, 2916 (1939).

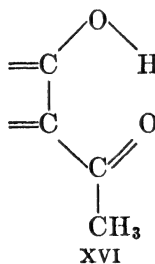
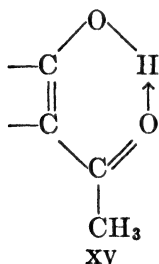
Fieser⁵⁰ found application of the diagnostic ozonization method to hydrindene to be complicated by the oxidation of a considerable amount of the hydrocarbon to α -hydrindone. From the part of the material which underwent normal ozonization, the only cleavage fragments isolated were those arising from the Kekulé form postulated by Mills and Nixon to have preferential stability. Under the conditions of the experiment



cyclopentanedione-1,2 is converted, probably through the enol, into succinic acid.

The observations as a whole show that, although there is no rigid fixation of bonds in the hydrindene system, a definite preference exists for one structure.

Other instances of a preferential stabilization of one Kekulé form are reported by Baker. From a study of various *o*-hydroxy-acetophenones, this investigator⁵¹ came to the conclusion that the formation of a six-membered chelate ring (p. 1868) containing coördinately linked hydrogen, as shown in formula XV, is dependent upon the presence of a double bond between the carbon atoms bearing the hydroxyl and acetyl groups.

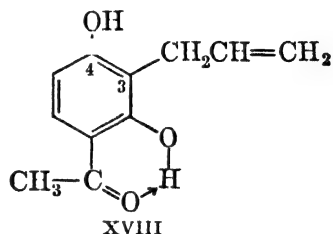
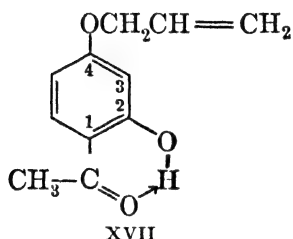


The conjugation of this double bond with that of the acetyl group apparently stabilizes the coördinate linkage, and if no double bond is available at this position, as in XVI, chelation does not occur. From these considerations it seemed possible that the formation of a chelate ring might

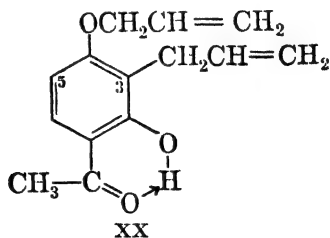
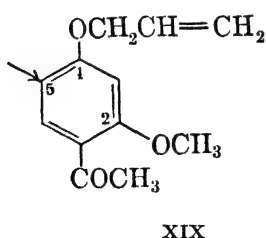
⁵⁰ Long and Fieser, *J. Am. Chem. Soc.*, **62**, 2670 (1940).

⁵¹ Baker, *J. Chem. Soc.*, 1684 (1934).

determine the Kekulé structure to a detectable extent, and in order to test this point Baker and Lothian⁵² investigated the Claisen rearrangement (p. 189) of the 4-allyl ether of resacetophenone, XVII. In this compound, chelation between the hydroxyl and acetyl groups would require the presence of a double bond in the 1,2-position, and consequently this would result in a stabilization of the Kekulé structure shown in the formula. The migration of an allyl group from oxygen to carbon



occurs with aliphatic enols as well as with phenols, and no reasonable mechanism for the reaction can be devised without assuming the participation of the double bond: $\text{—C(OCH}_2\text{CH=CH}_2\text{)=CH—} \rightarrow \text{—C(OH)=C(CH}_2\text{CH=CH}_2\text{)—}$. If the bond structure of the resacetophenone ether XVII is fixed as shown, the allyl group should migrate to the 3-position to give XVIII, and it was found that this isomer is indeed formed in not less than 85 per cent yield. That the course of the rearrangement is controlled by the chelation in the molecule was established by the results of an experiment with 2-O-methyl-4-O-allylresacetophenone, XIX. The replacement of the phenolic hydrogen atom by a methyl group makes chelation impossible, and consequently there should be no fixation of a Kekulé structure. On rearrangement of the ether it was found that the allyl group migrates largely to the 5-position, giving the usual type of symmetrically substituted product. The contrasting behavior of the free hydroxy compound, XVIII, therefore is of definite significance. In order to gain some idea of the extent of the bond fixation in chelated compounds, Baker and Lothian investigated the rearrangement of the



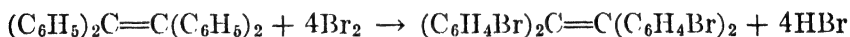
ether XX, in which the migration of the allyl group to the favored 3-position is prevented by the presence of a blocking group. The rear-

⁵² Baker and Lothian, *ibid.*, 628 (1935).

range of the substance proceeded somewhat slowly, but the fact that a reaction was observed shows that the bond structure is not entirely rigid. The unusual *ortho* substitution observed with XVII, however, shows that chelation can exert an influence in displacing the equilibrium between Kekulé tautomers, and similar observations were made in a study⁵³ of *o*-hydroxypropiophenones and *o*-hydroxybenzaldehydes.

The recognition of cases in which differences exist between alternate *ortho* positions in the nucleus is opposed to the idea that all six of the nuclear linkages in the ring are identical. The evidence cited constitutes a serious argument against all the many formulations embodying the concept of a centric structure. On the other hand, the feature of the Kekulé formula which originally was considered to be a weakness of this theory now appears to provide a means of accounting for phenomena which are not otherwise understandable.

Comparison of Benzene with Conjugated Compounds. Though the evidence above favors the Kekulé theory, there remains for consideration the problem of accounting for the inert character of benzene in terms of the cyclohexatriene formula. The classical objection that this formula appears to represent a condition of far greater reactivity than is actually observed was based originally on a comparison of benzene with simple substances such as ethylene and acetylene, and the differences in the nature of the characteristic reactions and in the reactivities are of course enormous. It has become apparent, however, that the double bond shows surprising differences in reactivity according to its environment (p. 631). An extreme illustration is that, although ethylene adds bromine with ease, the double linkage of tetraphenylethylene remains unattacked while bromine atoms enter the four phenyl groups.⁵⁴



In this highly substituted ethylenic hydrocarbon the relative reactivity of the simple types is reversed, possibly because of the conjugation of the double bond with the phenyl groups.

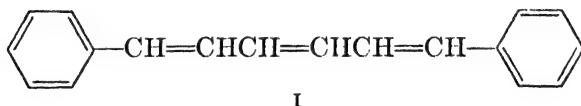
It is indeed rather with open-chain compounds which are conjugated that benzene is most properly compared. It may appear odd that the double bonds of benzene are inert to hydrogen bromide whereas this reagent adds easily to ethylene, but an entirely similar inertness is exhibited by diphenylbutadiene, $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}=\text{CHC}_6\text{H}_5$. Various conditions of reaction have been tried, but under no circumstances has

⁵³ Baker and Lothian, *ibid.*, 274 (1936).

⁵⁴ Biltz, *Ann.*, **296**, 231 (1897); Bauer, *Ber.*, **37**, 3321 (1904).

an addition of hydrogen bromide to this hydrocarbon been observed.⁵⁵ In a study of the properties and transformation products of the α -nitro derivative of diphenylbutadiene, Wieland and Stenzl⁵⁶ observed further indications of the relatively saturated character of the conjugated system of the compound and of the marked tendency of dihydro derivatives to revert to the more stable diene type. The substance may be said to possess definite "aromatic" characteristics.

Still more illuminating is the comparison afforded by the work of Kuhn and Winterstein⁵⁷ on the series of diphenylpolyenes of the general formula $C_6H_5(CH=CH)_n C_6H_5$. One of the most striking observations recorded is that these polyenes are all unusually resistant to oxidation by permanganate and that the most stable member of the series is diphenylhexatriene (I). The hydrocarbon is attacked hardly at all by permanganate in soda solution, and in acetone the triene is oxidized more slowly than diphenylethylene, diphenylbutadiene, or even diphenyloctatetraene. The difference in reactivity is by no means as great as that between benzene and cyclooctatetraene, but the results indicate that probably the length of the conjugated system is a factor of some importance. Diphenylhexatriene also resembles benzene in the stability



of the unsaturated system in comparison with the dihydride structure. The dibromide is not a stable substance but readily reverts to the triene type by the loss of bromine. On hydrogenation in the presence of palladium charcoal, the triene system is completely reduced and, as in benzene, intermediate di- and tetra-hydrides appear to be more easily reduced than the starting material, for they are not present in the mixtures obtained on partial hydrogenation. Using platinum oxide and a suitable solvent it is possible to hydrogenate also the phenyl groups at the ends of the chain. The rings are attacked somewhat less readily than the chain, but the difference is not great.

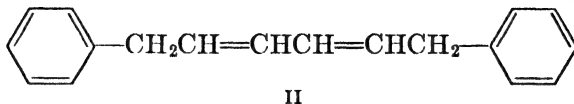
With the use of aluminum amalgam the diphenylpolyenes can be converted into dihydro compounds, the addition of hydrogen occurring at the ends of the open-chain conjugated system. Diphenylhexatriene (I), for example, yields dibenzylbutadiene, II. The dihydro derivatives such as II are highly reactive, easily polymerized substances, and they lack entirely the peculiar stability, or near-aromatic character, of the

⁵⁵ Hinrichsen, *Ann.*, **336**, 189 (1904); Zincke and Mühlhausen, *Ber.*, **38**, 757 (1905).

⁵⁶ Wieland and Stenzl, *Ann.*, **360**, 306 (1908).

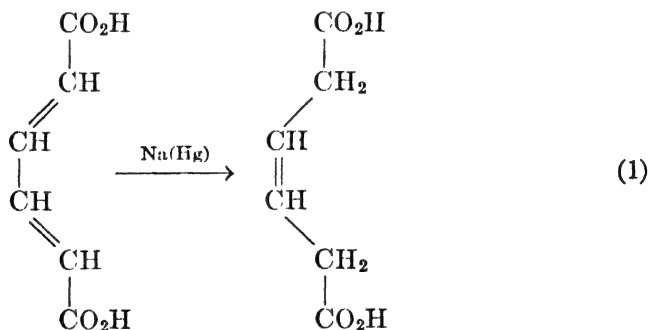
⁵⁷ Kuhn and Winterstein, *Helv. Chim. Acta*, **11**, 87 (1928).

more highly unsaturated compounds. The marked change in properties attending the reduction seems to be attributable to the fact that the addition of hydrogen breaks the conjugation of the original polyene system with the unsaturated centers in the terminal aromatic rings.

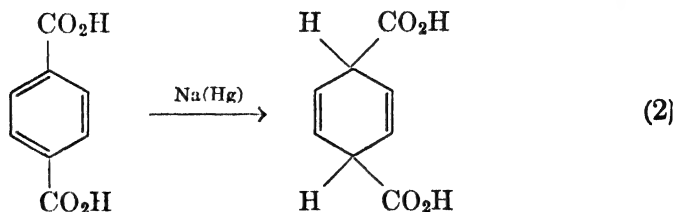


The new polyene system established in a dihydro derivative is separated from these rings by methylene groups and consequently occupies an isolated position in the chain. It is apparent that an open-chain polyene system attains maximum stability when it is conjugated with phenyl groups at the ends of the chain. It is but a step further to the more perfect conjugation of benzene, where the hexatriene system ends in itself. The special character of the aromatic ring perhaps is due largely to a type of conjugation which by its nature cannot be reproduced exactly among open-chain compounds.

In the aliphatic series, conjugation of a carbonyl group with an ethylenic linkage or a diene system often promotes, or appears to promote, reactions at these centers. Muconic acid, for example, is easily reduced by sodium amalgam and alcohol to the dihydride (1). Whether or not



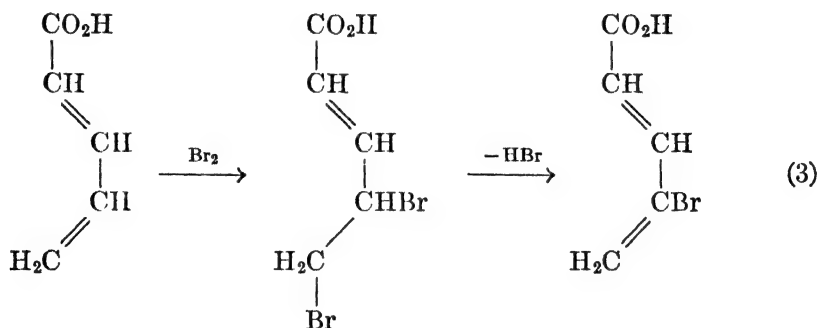
the reaction proceeds through a primary addition to the carbonyl groups, it finds an exact parallel, at least on the basis of the Kekulé formula, in the reduction of terephthalic acid by the same method (2). Another



example is in the forced Grignard reactions discovered by Gilman and by Kohler (p. 506), where a phenyl group conjugated with an unsaturated side chain participates in a 1,4-addition.

An interesting comparison of another sort is that 1-phenyl-4-amino-butadiene, $C_6H_5CH=CHCH=CHNH_2$, was found by Muskat⁵⁸ to resemble aniline in being stable in the amino, rather than the imino, form. Attempts to prepare eneamines, $>C=C(NH_2)-$, ordinarily yield instead the corresponding ketimines, $>CHC(=NH)-$. The same worker⁵⁹ found that bromine adds to the terminal bond of vinylacrylic acid and that the product easily loses hydrogen bromide to give the 3-bromo derivative (3). The series of reactions forms an interesting parallel to *meta* substitution in the benzene ring, as in the conversion of benzoic acid to the *m*-bromo derivative.

There is ample evidence that aromatic substances resemble open-chain conjugated compounds in many ways, and the objection that the Kekulé formula does not adequately represent the inert character of the ring largely vanishes when comparison is made with suitably constituted



compounds. Further exploration of open conjugated systems is highly desirable, for this may be expected to afford a further insight into the nature of the closed systems.

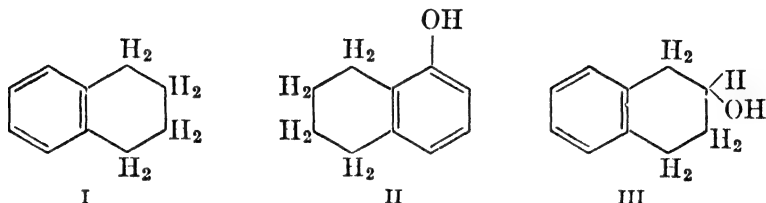
The Structure of Naphthalene. Much of the literature pertaining to the structure of naphthalene bears the imprint of a theoretical concept introduced by Bamberger⁶⁰ in summarizing the results of his classical studies of the reduction of naphthalene derivatives. Bamberger had found that naphthalene can be reduced easily to tetralin (I) by means of sodium and boiling amyl alcohol, and that the reaction stops with the introduction of four atoms of hydrogen. Under similar conditions α -naphthol is attacked almost entirely in the unsubstituted ring,

⁵⁸ Muskat and Grimsley, *J. Am. Chem. Soc.*, **55**, 3762 (1933).

⁵⁹ Muskat and co-workers, *ibid.*, **52**, 326, 812 (1930).

⁶⁰ Bamberger, *Ann.*, **257**, 1 (1890).

giving *ar*- α -tetralol (II), while β -naphthol yields chiefly *ac*- β -tetralol (III), a product of the alternate type. Because compounds of the naphthalene series can be reduced by reagents which leave an isolated benzene ring untouched, Bamberger regarded naphthalene as endowed with special properties which place it in a class distinct from benzene. He called attention to the peculiar character of the naphthols, which, in contrast to phenol, yield ethers on reaction with an alcohol and a



mineral acid. Such special properties vanish on partial hydrogenation, according to Bamberger, for the unsaturated ring of tetralin resists further reduction with sodium and therefore is truly benzenoid, and *ar*- α -tetralol (II) forms no ethers by the method indicated and is a true phenol. The ring of naphthalene which is susceptible to reduction is not aromatic, so the argument runs, and, since both rings appear to be identical, naphthalene contains no truly benzenoid, or aromatic, rings. Bamberger concluded that naphthalene is fundamentally different from benzene and must be assigned some special formula.

The argument appears fallacious because it confuses differences in degree with differences in kind. The differences cited are merely manifestations of a greater reactivity of the naphthalene system as compared with the isolated benzene nucleus. There is considerable variation in reactivity in the benzene series itself, and the line of demarcation is not as sharp as was at one time supposed. Though the formation of ethers under the conditions of the Fischer esterification reaction is in general characteristic of naphthols and not of phenols, the presence of activating groups may render a compound of the benzene series capable of entering into the reaction. This is true, for example, with phloroglucinol.⁶¹ Another supposedly special property is that α - and β -naphthylamine couple directly with diazonium salts to give aminoazo compounds, whereas primary amines of the benzene series usually give diazoamino compounds in the initial reaction and yield azo derivatives only by the subsequent rearrangement of the product. In a discussion of the coupling reaction given later in this chapter, reference will be made to the observation that direct coupling may be achieved also in the benzene series by selecting

⁶¹ Will and Albrecht, *Ber.*, **17**, 2106 (1884); Weidel and Pollak, *Monatsh.*, **21**, 22 (1900)

suitable conditions or by using sufficiently reactive components, and it is clear that no fundamental difference is involved. The only significance to be attached to these and other interesting comparisons is that the unsaturated system of naphthalene is more reactive, more susceptible to attack, than that of benzene. Naphthalene is characterized by a generally greater susceptibility to oxidation, reduction, and substitution, particularly in the α -position, but there is no more justification for attempting to represent these facts by means of a special formulation than there would be for a particularly reactive benzene homolog. The fact that the carbonyl group of a ketone is more reactive than that of an ester is not a sufficient reason for supposing that the kind of unsaturation is different in the two compounds.

Bamberger even went so far as to use different formulations for α - and β -naphthol because of the different direction of the reduction in the two cases, but further hydrogenation studies have eliminated any experimental basis for such a hypothesis. By the selection of suitable catalysts, β -naphthol can be tetrahydrogenated in either ring.⁶² The course of the catalytic hydrogenation of the hydrocarbon itself can be summarized in the following statements. With nickel catalysts naphthalene is converted first into tetralin and then, more slowly, into decalin. Platinum catalysts usually give similar results, but Willstätter⁶³ found that, with one particular type of catalyst containing very little oxygen, decalin was produced directly from naphthalene without the intermediate formation of tetralin. Zelinsky⁶⁴ found, conversely, that decalin on partial dehydrogenation at 300° yielded naphthalene and unchanged decalin, but no tetralin. To the extent that such reactions can be relied upon, they afford some indication that naphthalene has a symmetrical structure.

Although reduction and hydrogenation studies have figured even more prominently in the theoretical discussions of the literature than is indicated by the brief review given above, they cannot be said to have contributed greatly to the solution of the problem. Attempts have been made to deduce the structure from quantum mechanics,⁶⁵ and from studies of various physical properties of naphthalene derivatives, including molecular refractions,⁶⁶ dipole moments,⁶⁷ ⁶⁸ dissociation constants,⁶⁸ ab-

⁶² Hückel, *Ann.*, **451**, 109 (1926).

⁶³ Willstätter and Hatt, *Ber.*, **45**, 1480 (1912); Willstätter and Seitz, *Ber.*, **56**, 1388 (1923).

⁶⁴ Zelinsky, *Ber.*, **56**, 1723 (1923).

⁶⁵ Pauling and Wheland, *J. Chem. Phys.*, **1**, 362 (1933).

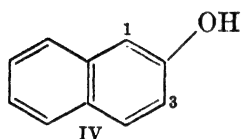
⁶⁶ v. Auwers and Frühling, *Ann.*, **422**, 206 (1921); v. Auwers and Krollpfeiffer, *Ann.* **430**, 243 (1923).

⁶⁷ Hampson and Weissberger, *J. Chem. Soc.*, 393 (1936).

⁶⁸ Bergmann and Hirshberg, *ibid.*, 331 (1936).

sorption spectra,⁶⁹ and Raman and infrared spectra,⁷⁰ but the results have not been decisive.

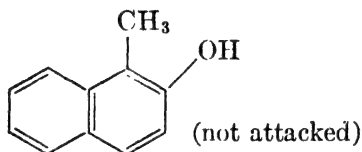
A chemical criterion of the structure was recognized by Marckwald⁷¹ in 1893. Marckwald called attention to the marked difference between the two positions *ortho* to the functional group of β -naphthol or β -naphthylamine, and he observed that the symmetrical Kekulé formula for naphthalene suggested by Erlenmeyer (1866) provides a rational interpretation of the difference. As applied to β -naphthol, this formula (IV)



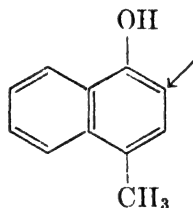
indicates that the *ortho* carbon atom at position 1 is joined by a double bond to the atom carrying the functional group, while the connection between the alternate *ortho* position 3 and position 2 is by means of a single linkage. One *ortho* carbon atom

is part of an enolic unit, while the other is not, and, if the bonds are immobile, the difference in the functions of the two *ortho* positions is easily understandable. Many facts have accumulated in support of the view that there is a double bond at the 1,2-position and a single bond at C₂-C₃.

One line of evidence is from the coupling reaction, or rather from its failure in certain specific cases. β -Naphthol couples at position 1, but if this position is blocked by a stable group (alkyl), as in V, no coupling with diazotized amines occurs. A less stable group (carboxyl, halogen) at the 1-position is displaced by the reagent, and in no case is the other *ortho* position attacked. The failure of V to react cannot be ascribed

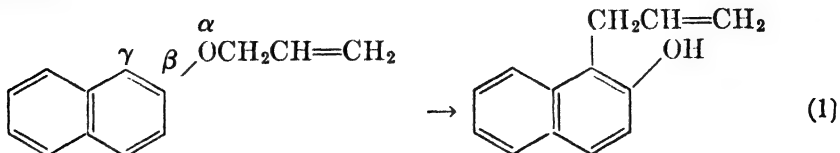


V



VI

to the known lower degree of reactivity of the β -positions of naphthalene in comparison with the α -positions, for 4-methyl-1-naphthol (VI) couples easily in the β -position, C₂. It is not merely a difference in the degree of reactivity which is involved, but a difference in kind, and the only

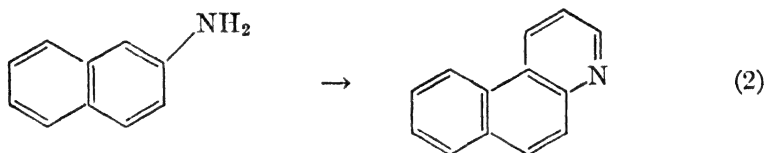


⁶⁹ de Laszlo, *J. Am. Chem. Soc.*, **50**, 892 (1928).

⁷⁰ Kohlrausch, *Ber.*, **68**, 893 (1935).

⁷¹ Marckwald, *Ann.*, **274**, 331 (1893); **279**, 1 (1894).

plausible explanation is that the double bond required in some way for the coupling is available at one position and not at the other. The conversion of β -naphthyl allyl ether into 1-allyl-2-naphthol by the Claisen reaction (1) represents a substitution by way of an intramolecular rearrangement (p. 189), and it conforms to the same rules. An alkyl substituent at the 1 position effectively prevents the rearrangement.⁷² If the reaction is considered to consist in an α,γ shift, it may be said that the failure of a 1-substituted ether to rearrange shows that the carbon atom at position 3 cannot form the end of an α,γ system, and hence that the double bond is incapable of migrating to the 2,3-position, even at the boiling point of the ether. The Skraup reaction, which may involve still another type of substitution, formed the central point in Marckwald's⁷¹ discussion of the problem. The pyridine ring produced in the Skraup reaction of β -naphthylamine with glycerol, sulfuric acid, and an oxidizing



agent (2), extends to position 1 and not 3, and Marckwald found that in similarly constituted compounds a methyl group at position 1 prevents the reaction while a bromine atom may be displaced. Apparently there is a general disposition for cyclization to occur in such a way that the new ring includes a double bond of the original ring system, although Fries⁷³ has noted that this is not an invariable rule, for 1-chloro-2-naphthylamine yields a considerable amount of the linear tricyclic compound in which the chlorine atom is intact.

Further evidence of a fixed bond structure in at least a part of the naphthalene molecule is furnished by reactions involving the replacement or modification of a functional group rather than a nuclear substitution. An interesting case is the etherification of naphthols with an alcohol, using an acid catalyst (3).⁷⁴ * Davis⁷⁵ found that the etherification is almost completely stopped by a halogen atom or a nitro group in the 1-position, and Fieser and Lothrop⁷⁶ observed that alkyl groups in this position also strongly inhibit the reaction. It was found that the effect of substitution at the alternate *ortho* position 3 is of an entirely

⁷² Claisen, *Ber.*, **45**, 3157 (1912).

⁷³ Fries, *Ann.*, **516**, 285, footnote (1935).

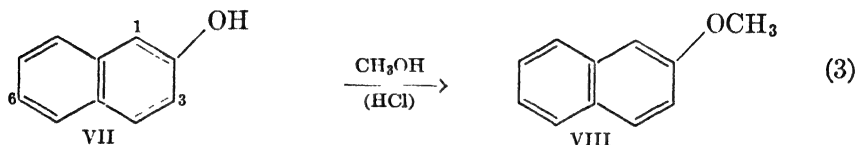
⁷⁴ Liebermann and Hagen, *Ber.*, **15**, 1427 (1882).

* The conversion of naphthols into dinaphthyl ethers, observed by Graebe, *Ber.*, **13** 1849 (1880), probably is a modification of the same reaction.

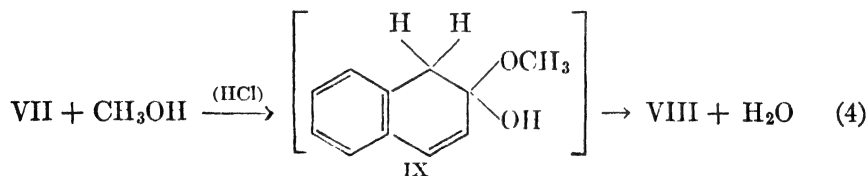
⁷⁵ Davis, *J. Chem. Soc.*, **77**, 33 (1900).

⁷⁶ Fieser and Lothrop, *J. Am. Chem. Soc.*, **57**, 1459 (1935).

different nature. An alkyl group at C_3 actually promotes the etherification reaction, and the influence is about the same when the alkyl group is located at position 6 in the adjoining nucleus. A bromine atom impedes the reaction to some extent when it occupies either the 3- or the 6-position. The influence of a substituent at C_3 therefore appears to be of a chemical, and not of a stereochemical, nature. The proximity in space



of the substituent to the hydroxyl group evidently is not a factor of importance. An apparently related observation is that *p*-nitrophenol fails completely to react under conditions sufficient for accomplishing a partial etherification of phenol itself.⁷⁷ From the limited information available, it appears that groups which facilitate ordinary aromatic substitutions promote the etherification when located at certain positions other than C_1 , whereas groups which retard aromatic substitutions (*m*-directing groups and halogen atoms) have the opposite effect. Substituents of both types, however, effectively block the etherification when located at position 1. It may be inferred that this blocking is not ordinary steric hindrance, for it occurs only when the group in question is situated at one of the two *ortho* positions. That one of these positions has double-bond characteristics which the other lacks seems to provide an adequate basis for interpreting the difference. A mechanistic explanation of the etherification reaction was suggested by Henry⁷⁸ and extended by Wegscheider,⁷⁷ who supposed that an intermediate addition product is formed



and subsequently loses water (4). If alcohol indeed adds to the 1,2-double bond, the blocking effect of a substituent attached to this linkage at the 1-position would be understandable.

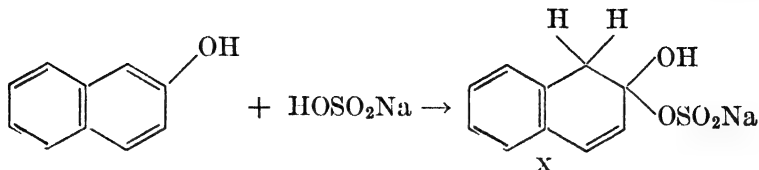
While formula IX represents an intermediate which is purely hypothetical, Bucherer⁷⁹ isolated an addition product from β -naphthol and

⁷⁷ Wegscheider, *Monatsh.*, **16**, 75 (1895); **18**, 629 (1897).

⁷⁸ Henry, *Ber.*, **10**, 2041 (1877).

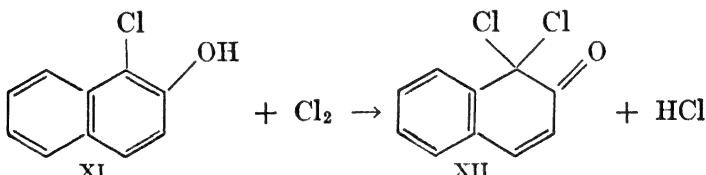
⁷⁹ Bucherer, *J. prakt. Chem.*, **69**, 49 (1904).

sodium bisulfite which Vorozhtzov⁸⁰ regarded as having an analogous structure, X. The substance may be an intermediate in the amination



of β -naphthol with bisulfite and ammonia (Bucherer reaction), and it is possible that the conversion of β -naphthol into β -naphthylamine with ammonia alone involves a similar addition. Here, an alkyl group at the 1-position should inhibit the reaction. Vorozhtzov has pointed out that the failure of phenol to react with ammonia in the manner of the naphthols is merely because the mononuclear compound does not possess the requisite reactivity. Amination can be accomplished with the more reactive phloroglucinol.

Convincing evidence that the double bonds of naphthalene are not free to migrate is furnished by the extensive series of investigations initiated by Th. Zincke and extended by Fries on the halogenation of naphthols and naphthylamines. A *p*-alkyl phenol with two free *ortho* positions is halogenated first at one of these positions and then at the other. If the first reaction in some way involves an enolic double bond, it is evident that the second substitution is preceded by the migration of the double bonds in such a way as to provide an enolic grouping suitable for this reaction. In contrast to this behavior, 1-chloro-2-naphthol does not form a 1,3-dihalo derivative but yields instead the ketohalogenide XII.^{81, 82} Zincke interpreted the reaction as involving an addition to the 1,2-double bond, and, if this interpretation is correct, it may be said that



the halogen molecule, finding no such linkage at $\text{C}_2\text{-C}_3$, adds in this manner even though a blocking substituent is present. Fries⁸³ has noted that the velocity of addition to —CCl=C(OH)— probably is less than to —C(OH)=CH— , were the latter system available. The overall reac-

⁸⁰ Vorozhtzov, *Bull. soc. chim.*, [4] **35**, 996 (1924).

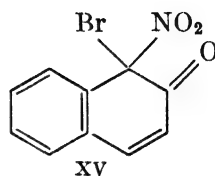
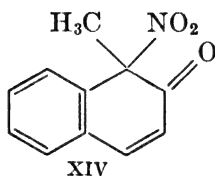
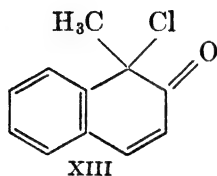
⁸¹ Zincke, *Ber.*, **21**, 3378, 3540 (1888).

⁸² Fries and Schimmelschmidt, *Ann.*, **484**, 245 (1930).

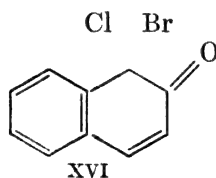
⁸³ Fries, *Ann.*, **454**, 121 (1927).

tion represents an equilibrium process, for Fries and Schimmelschmidt⁸² found that the transformation pictured in the formulas can be reversed by the action of hydrogen chloride and a halogen acceptor.

Many other ketones of analogous structure have been isolated and thoroughly characterized. The methylketochloride XIII is obtained⁸⁴



by the chlorination of 1-methyl-2-naphthol, while the nitro ketones XIV and XV result from the action of nitric acid on the 1-substituted naphthols.⁸⁵ The ketonitro bromide XV is converted smoothly into β -naphthoquinone when a solution of the substance in benzene is warmed gently.⁸⁶ An interesting member of the series is the mixed halogenide XVI, which has been prepared from both 1-bromo- and 1-chloro-2-



naphthol.⁸² That the same compound results in each case eliminates the possibility that one of the halogen atoms is attached to oxygen. The hypohalite formulation for the type of compound under discussion is excluded by an abundance of other evidence, for example that furnished by Zincke's⁸⁷ exhaustive study of the further halogenation and alkaline cleavage of the keto dichloride XII. On treating the mixed halogenide XVI with zinc and acetic acid to effect reversion to an aromatic structure, the more reactive bromine atom is eliminated in preference to chlorine. Among other extensions of the abundant experimental evidence in this field which points to a fixation of the bond structure of naphthalene is the further study of the homo- and heteronuclear halogenation of β -naphthol conducted by Fries and Schimmelschmidt.^{82, 88}

The ketonic substance XIX represents the product of a different type of reaction and belongs to the 1,4- rather than the 1,2-dihydronaphthalene

⁸⁴ Fries and Hempelmann, *Ber.*, **41**, 2614 (1908).

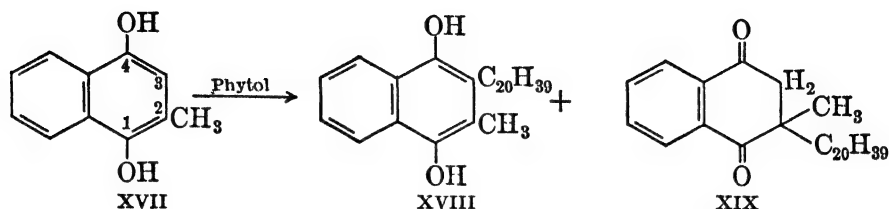
⁸⁵ Fries and Hübner, *Ber.*, **39**, 435 (1906).

⁸⁶ Fries, *Ann.*, **389**, 315 (1912).

⁸⁷ Zincke, *Ber.*, **21**, 3378, 3540 (1888).

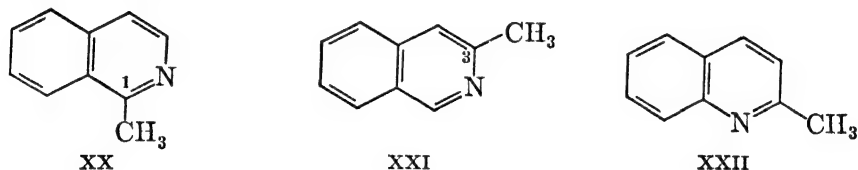
⁸⁸ See also Bell, *J. Chem. Soc.*, 2732 (1932).

series. The compound was isolated⁸⁹ as a by-product of the synthesis of vitamin K₁ hydroquinone (XVIII), from methylnaphthohydroquinone and phytol in the presence of oxalic acid. The by-product evidently arises from some form of addition of the reactive β,γ -unsaturated alcohol



to the 1,2-bond of the starting material, and the formation of the normal product XVIII may be the result of an addition at the 3,4-position.

A different method of probing for centers of unsaturation which involves no disturbance of these centers was developed by Mills and Smith.⁹⁰ The location of the $>\text{C}=\text{N}-$ bond of the isoquinoline nucleus



was established by noting its activating influence on a methyl group at C₁, and the absence of such an influence on a methyl group at C₃. 1-Methylisoquinoline (XX) condenses with benzaldehyde and other reagents, while the 3-isomer (XXI) is incapable of entering into such reactions. The activity of the methyl group of quinaldine (XXII) likewise can be attributed to the presence of a C : N linkage in the position shown.⁹¹ The observations indicate that quinoline and isoquinoline are analogous in structure to naphthalene.

The extensive and varied evidence leaves little ground for questioning the conclusion that the two *ortho* positions of β -naphthol differ in kind. The only rational interpretation that has been given of this striking fact is that the double and single bonds in a Kekulé ring are fixed in the α,β - and β,β -positions, respectively.

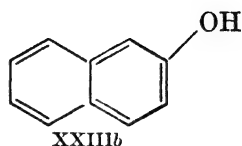
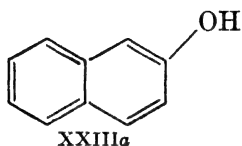
The establishment of the positions of the unsaturated centers in one part of the naphthalene molecule does not settle the problem of the complete bond structure. The facts cited may be explained on the basis

⁸⁹ Tishler, Fieser, and Wendler, *J. Am. Chem. Soc.*, **62**, 1982 (1940)

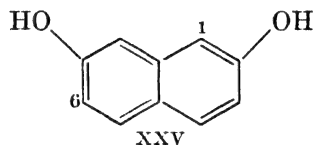
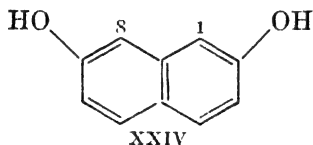
⁹⁰ Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

⁹¹ Henrich, *Ber.*, **32**, 668 (1899).

of either the symmetrical formula used above or the unsymmetrical structure XXIIIa, although in the latter case some additional assumption would be required regarding the failure of the substance to exist in the alternate unsymmetrical form XXIIIb. Fieser and Lothrop⁷⁶ ex-



tended to 2,6- or 2,7-dihydroxynaphthalene methods of investigation employed in the case of β -naphthol. If 2,7-dihydroxynaphthalene has the fixed symmetrical structure XXIV, it should be attacked by substituting agents at the two enolic *ortho* positions 1 and 8, but if it has the

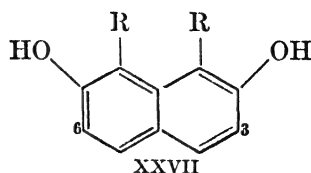
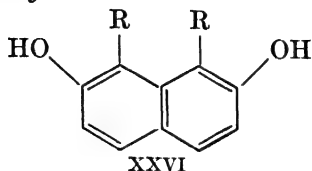


unsymmetrical structure XXV the disubstitution should occur at the 1- and 6-positions. Actually, coupling occurs at the 1- and 8-positions,⁹² but one might reconcile the observation with the unsymmetrical formula XXV by supposing that the first substituent enters at C₁ and that the bonds then shift to the alternate unsymmetrical arrangement and provide an enolic group at C₇-C₈ for the entrance of the next azo group. The same interpretation might be given of the observation that 2,7-dihydroxynaphthalene is converted into a dimethyl ether on treatment with methanol and an acid catalyst, although on face value this result seems to favor a symmetrical formulation.⁹³ In order to settle the matter unequivocally, Fieser and Lothrop investigated various 1,8-dialkyl derivatives of 2,7-dihydroxynaphthalene. If such a compound has the symmetrical structure XXVI, it should be incapable of *ortho* substitutions in the free positions 3 and 6, but if it exists in the form XXVII, or if it can tautomerize to this form having an available enolic *ortho* position at C₆, monosubstitution should be possible. Compounds of this type, as well as various 1,5-dialkyl-2,6-dihydroxynaphthalenes, were tested for phenolic properties with entirely negative results. They do not couple, and their allyl ethers do not rearrange. This evidence indicates that the naphthols have the symmetrical structure of the Erlenmeyer formula and

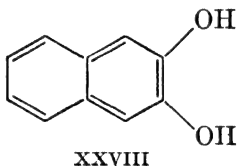
⁹² Ruggli and Courtin, *Helv. Chim. Acta*, **15**, 110 (1932).

⁹³ v. Weinberg, *Ber.*, **54**, 2168 (1921).

that the arrangement of the bonds represents a condition of considerable rigidity.



One further piece of chemical evidence which has reference to the bond structure as a whole is the failure of 2,3-dihydroxynaphthalene to yield a quinone on oxidation. The observation was cited first by Marckwald,⁷¹ and in recent years it has been demonstrated both by chemical⁹⁴ and electrochemical⁹⁵ evidence that this is not due to the lack of stability of the hypothetical 2,3-naphthoquinone, for it is never produced, but rather to the formation as a primary oxidation product of a univalent-oxygen free radical. The two hydroxyls function independently and not, as when the carbon atoms holding such groups are connected by means of a double bond, as a unit. The compound does



not appear capable of existing in the unsymmetrical form (XXVIII) having an enediol grouping. Fries and Bestian⁹⁶ have found 4,5-divinylcatechol to be similarly resistant to quinone formation, an observation which they interpret as indicating bond fixation approaching that of the naphthalene derivative.

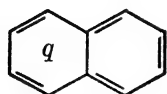
The evidence cited indicates that naphthalene has the symmetrical structure and differs from benzene in having a more rigid and a more reactive conjugated system of linkages. The reason for these differences is a separate problem. A simple and plausible solution has been suggested by Fries.⁸³ Naphthalene, he considers, has little tendency to exist in the unsymmetrical form because one of the rings would then have to depart from the aromatic condition and acquire the bond structure of the highly reactive *o*-benzoquinone, or the character of the thermodynamically unstable 1,2-dihydrobenzene. The resistance to the acquisition of quinonoid or dihydride characteristics accounts for the lack of stability of

⁹⁴ Fries and Schimmelschmidt, *Ber.*, **65**, 1502 (1932).

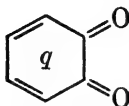
⁹⁵ Fieser, *J. Am. Chem. Soc.*, **52**, 5219 (1930).

⁹⁶ Fries and Bestian, *Ann.*, **533**, 72 (1937).

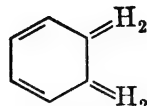
this structure. In the Erlenmeyer formula neither ring is perhaps an entirely true benzenoid nucleus because the central bond is shared between the two rings and conjugated in different directions, but each approaches as nearly as possible the stable condition of an isolated ben-



Unstable



Reactive



Unstable

zene ring. The tendency to approach this condition, which appears to be the most important feature characteristic of the aromatic state, results, in the case of naphthalene, in the suppression of oscillation.⁹⁷

The factor recognized by Fries as determining the bond structure of naphthalene is operative as well in other polynuclear aromatic compounds, and it will be convenient to refer to the important generalization in the discussions which follow as the Fries rule. This rule states that each aromatic ring of a polynuclear compound tends to assume the bond structure which most nearly approaches the condition of an isolated benzene ring.

The enhanced reactivity or unsaturation of naphthalene, as compared with benzene, is manifested particularly in the α -positions of the molecule. The greater susceptibility to attack is indicated by the occurrence of reactions under conditions such that benzene remains largely unaltered. Naphthalene, for example, can be oxidized to 1,4-naphthoquinone in appreciable yield (16 per cent),⁹⁸ and it is converted into 1,4-dihydronaphthalene by the action of sodium and alcohol.⁹⁹ The point is demonstrated further in competitive reactions, for example, by the observation¹⁰⁰ that the condensation of naphthalene with phthalic anhydride can be conducted in benzene solution with no appreciable contamination of the naphthoylbenzoic acid with benzoylbenzoic acid. In these reactions, as in most substitutions, the α -positions are attacked preferentially. Fries⁹⁷ expressed the view that the restriction to the migration of the bonds is directly responsible for the increased ease of reaction. The double bond shared between the rings, he notes, is subject to valence claim from two directions, and an equalization of valence in the two rings cannot be attained as fully as in an isolated benzenoid ring. In consequence, the two nuclei are less aromatic and more unsaturated than true benzene rings.

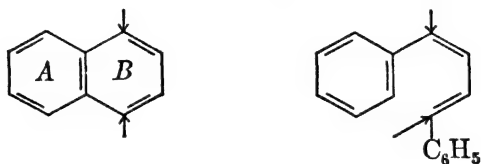
⁹⁷ Fries, Walter, and Schilling, *Ann.*, **516**, 248 (1935).

⁹⁸ Plimpton, *J. Chem. Soc.*, **37**, 634 (1880); Japp and Miller, *ibid.*, **39**, 220 (1881).

⁹⁹ Bamberger and Lodter, *Ber.*, **26**, 1833 (1893); Straus and Lemmel, *Ber.*, **46**, 232 (1913).

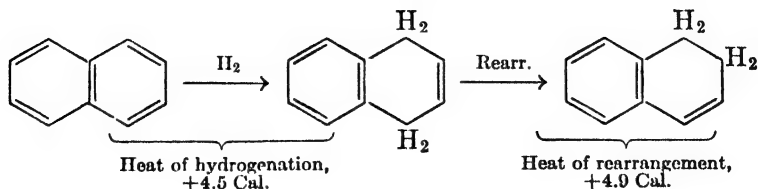
¹⁰⁰ Heller and Schülke, *Ber.*, **41**, 3633 (1908).

The mere proximity of the α -position in one nucleus, but not the β -position, to an adjoining aromatic ring, may be a factor of some importance in contributing to the reactivity at this position, and such an effect would not necessarily be associated with the bond fixation. It is evident from halogenation experiments that in ethylbenzene or tetralin the α -position, but not the β -position, of the side chain or alicyclic ring is activated by the unsaturated benzenoid nucleus. Although it is not easy to interpret a comparison between saturated and unsaturated side rings, some α -activation in the case of naphthalene seems possible. An enlightening comparison of strictly additive reactions involving unsaturated systems may be made between the reduction of naphthalene with sodium and alcohol⁹⁹ and the reduction of 1,4-diphenylbutadiene, and of other diphenylpolyenes, with aluminum amalgam.⁵⁷ In each reduction, hydro-



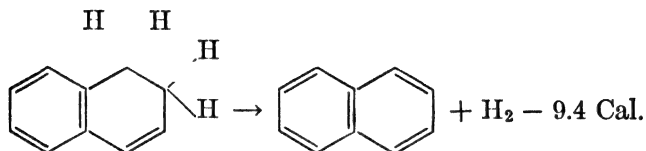
gen adds to the ends of a conjugated system, as indicated by the arrows, and the reaction then stops. 1,4-Dihydronaphthalene is reducible to tetralin by the reagent employed only after rearrangement to the 1,2-dihydride. In the diphenylpolyenes, which in general chemical properties bear much more than a superficial resemblance to naphthalene, the reactive positions are at the two ends of the conjugated aliphatic system terminating in benzene rings. In naphthalene the centers of special reactivity are similarly situated, for the conjugated system present in ring B is also anchored at the two ends, in this case into the same aromatic nucleus (A). The two hydrocarbons appear to be analogous in structure and in their behavior on reduction, and possibly the same factors are involved in determining their properties.

One further inference concerning naphthalene may be drawn from the thermochemical data pertaining to the hydrocarbon and its dihydro derivatives.¹⁰¹ As stated above, naphthalene on reduction is attacked at the 1,4-positions, and the reaction is slightly exothermic. The 1,4-



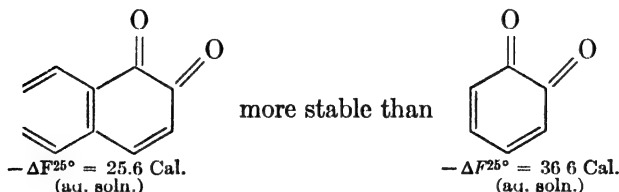
¹⁰¹ Roth and v. Auwers, *Ann.*, **407**, 172 (1915).

dihydride is not a very stable compound, for the alicyclic double bond occupies an isolated position, and this easily migrates to a more stable position conjugated with the unreduced nucleus. The rearrangement is attended with the liberation of heat. Stated in another way, the data show that the conversion of 1,2-dihydronaphthalene into naphthalene is an endothermic process. The heat of dehydrogenation is only about



one-third that required for the establishment of an aliphatic ethylenic linkage, but the point of greatest significance is that this aromatization requires a fairly considerable input of energy, whereas the aromatization of 1,2-dihydrobenzene is an exothermic reaction (p. 119). Though many substituted dihydro derivatives of benzene probably are thermodynamically unstable with respect to the fully aromatic structures to which they can revert, it appears that this is not true in the naphthalene series, and consequently a simple explanation is available for the existence of dihydronaphthalene derivatives of types rarely encountered in the benzene series, and for the frequent occurrence of reactions which seem to proceed through an intermediate addition product of dihydride structure.

The relatively greater stability of 1,2-dihydronaphthalene, with respect to the aromatic structure, than of 1,2-dihydrobenzene, is easily accounted for. The dihydrides have the nuclear bond systems of β -naphthoquinone and of *o*-benzoquinone, respectively, and an accurate measure of the relative stability of the systems is available in the oxidation-reduction potentials of the quinones. The pertinent data are included in Table I, along with values for the potentials of various quinones derived from polynuclear hydrocarbons. That β -naphthoquinone has a lower potential than *o*-benzoquinone means that it has less tendency to undergo reduction, that its quinonoid ring is more stable and less prone to change



to the aromatic condition which it acquires in the hydroquinone. The free energies of reduction, calculated from the expression $-\Delta F = nFE_0$, are appended to the formulas, and it is seen that the fusing of a benzene

ring to one of the ethylenic linkages of the mononuclear quinone results in a great diminution in the driving force of the reduction, or in a stabilization of the molecule. The result is easily understood, for an ethylenic linkage which in the benzoquinone is highly unsaturated, and which therefore contributes to the reactivity of the quinonoid system as a whole, is, in the naphthoquinone, incorporated in a benzenoid ring and rendered comparatively inert.

The same explanation applies to the similarly constituted dihydrides. The highly reactive 1,2-dihydrobenzene is stabilized when one of the alicyclic double bonds is shared with a benzene ring. The free energy of reduction of β -naphthoquinone is 11.0 Cal. less than that of *o*-benzoqui-

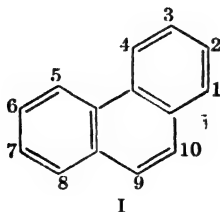
TABLE I
REDUCTION POTENTIALS OF QUINONES (25°)

| | Normal Potential E_0 , volts | |
|--------------------------------------|--------------------------------|---------------------------|
| | Aq. Soln. | Alc. Soln. |
| <i>p</i> -Benzoquinone..... | 0.699 | 0.715 ^a |
| <i>o</i> -Benzoquinone..... | .794 ^b | |
| α -Naphthoquinone..... | .470 ^c | .484 ^d |
| β -Naphthoquinone..... | .555 ^d | .576 ^b |
| 2,6-Naphthoquinone..... | | .76 (calcd.) ^e |
| 1,4,5,8-Naphthodiquinone..... | | (.972) ^f |
| Diphenoquinone..... | | .954 ^a |
| Stilbenequinone..... | | .854 ^a |
| 9,10-Phenanthrenequinone..... | | .460 ^g |
| 1,4-Phenanthrenequinone..... | | .523 ^g |
| 1,2-Phenanthrenequinone..... | | .660 ^b |
| 3,4-Phenanthrenequinone..... | | .621 ^b |
| 9,10-Anthraquinone..... | | .154 ^h |
| 1,2-Anthraquinone..... | | .490 ⁱ |
| 1,4-Anthraquinone..... | | .401 ^j |
| 1,2-Benz-9,10-anthraquinone..... | | .228 ^k |
| 1,2-Benz-3,4-anthraquinone..... | | .430 ^k |
| 1,2,5,6-Dibenz-9,10-anthraquinone... | | .268 ^k |
| 5,6-Chrysenequinone..... | | .465 ^k |
| 6,12-Chrysenequinone..... | | .392 ^k |

^a Fieser, *J. Am. Chem. Soc.*, **52**, 4915 (1930); ^b Fieser and Peters, *ibid.*, **53**, 793 (1931); ^c LaMer and Baker, *ibid.*, **44**, 1954 (1922); ^d Fieser and Fieser, *ibid.*, **56**, 1565 (1934); ^e Fieser, *ibid.*, **52**, 5204 (1930); ^f estimated from the potential referred to the quinhydrone electrode in acetic acid solution at 20° [Dimroth, *Angew. Chem.*, **46**, 571 (1933)]; ^g Fieser, *J. Am. Chem. Soc.*, **51**, 3101 (1929); ^h Fieser and Peters, *ibid.*, **53**, 4080 (1931); ⁱ Conant and Fieser, *ibid.*, **46**, 1858 (1924); ^j Fieser, *ibid.*, **50**, 465 (1928); ^k Fieser and Dietz, *ibid.*, **53**, 1128 (1931).

none, and it is of interest that the heat effect in the aromatization of 1,2-dihydronaphthalene by the elimination of two atoms of hydrogen is 15.0 Cal. less than for the corresponding reaction of 1,2-dihydrobenzene. Considering that the heats of reaction are subject to some uncertainties, that the entropies in the dehydrogenations may not be identical, and that a comparison is made between reactions occurring in different states, the correspondence in the values for the energy changes is about as good as could be expected. The degree of aromaticity of a polynuclear hydrocarbon seems to be determined by the relative stability of the unsaturated structure with respect to its hydro derivatives, and it is a matter of considerable importance that accurate information on this point can be obtained from oxido-reduction potential data for the corresponding quinones. In using such data it is necessary only to make sure that the comparison is not invalidated by some disturbing factor. It would not be proper, for example, to attempt to predict the relative stabilities of 1,2- and 1,4-dihydronaphthalene from the relationships between β - and α -naphthoquinone, because the character of the former compounds is dependent in part upon whether the double bond is isolated in the reduced ring or conjugated with the benzenoid nucleus, whereas in the quinones the corresponding double bond does not in either case occupy an isolated position but is conjugated with at least one carbonyl group. Since the structural relationships are quite different, a comparison is meaningless. Actually the 1,4-quinone is more stable than the 1,2-quinone in both the benzene and naphthalene series, while the reverse is true of the 1,4- and 1,2-dihydro compounds. *Ortho* and *para* quinones differ in the manner in which the carbonyl groups are conjugated, and a comparison between compounds of the two types is valid only if account is taken of this difference.

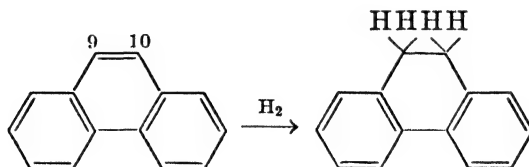
Phenanthrene. Four Kekulé bond structures for phenanthrene are theoretically possible, but according to the Fries rule (p. 156) one of these would be expected to surpass the rest in stability. This structure, illustrated in formula I, is symmetrical, and each ring has associated with



it the full complement of three double bonds, as in benzene, although there is some sharing of double linkages. In the alternate formulas one or more of the rings has an *o*-quinonoid or a tetrahydride structure and

thus departs more widely from the stable benzenoid condition. There is evidence that the formula expected from theoretical considerations to represent the stable state of the molecule corresponds to the true structure. Fieser and Young¹⁰² found that, while the coupling of 2-phenanthrol and the rearrangement of its allyl ether normally lead to substitution in the 1-position, the reactions are effectively blocked by an alkyl group at this position. A blocking group at the 4-position similarly interferes with the phenolic functioning of 3-phenanthrol, and from these observations it seems clear that double bonds are located at the 1,2- and 3,4-positions and that the bond structure in this part of the molecule is as rigid as in naphthalene.

Phenanthrene is more susceptible to oxidation and reduction than naphthalene, and the point of first attack in each reaction is at the 9- and 10-positions. The only factor which seems to limit the yield of the 9,10-quinone is the sensitivity of this compound to further oxidation, and the 9,10-dihydride can be obtained in nearly quantitative yield by hydrogenation in the presence of copper-chromium oxide at a moderate temperature.¹⁰³ It is significant that this catalyst is not active toward



benzene or naphthalene and that the selective hydrogenation of phenanthrene occurs under conditions not much more drastic than are required for the hydrogenation of ethylenic hydrocarbons of the aliphatic or alicyclic series. A further striking indication of the olefinic character of the 9,10-double bond is that phenanthrene forms a stable 9,10-dibromide. A possible factor contributing to the unusual reactivity manifested in the central ring of the hydrocarbon is that each of the adjacent carbon atoms 9 and 10 occupies an α -position with respect to a terminal aromatic ring; these unsaturated rings may exert an activating influence, as suggested in the case of naphthalene. This conception, though perhaps a crude one, is of value in understanding the course of some of the substitution reactions. In the sulfonation of phenanthrene, and in the Friedel and Crafts condensations conducted in nitrobenzene solution, substitution occurs chiefly at the 3- and 2-positions, rather than in the reactive central nucleus. These are β -positions, and it will be recalled

¹⁰² Fieser and Young, *J. Am. Chem. Soc.*, **53**, 4120 (1931).

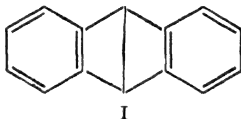
¹⁰³ Burger and Mosettig, *ibid.*, **57**, 2731 (1935); **58**, 1857 (1936); Durland and Adkins *ibid.*, **59**, 135 (1937); **60**, 1501 (1938).

that in the case of naphthalene there is some avoidance of the reactive α -positions in substitutions, in contrast to reactions of oxidation and reduction. β -Substitution predominates in the high-temperature sulfonation of naphthalene and in some of the Friedel-Crafts reactions in nitrobenzene solution.

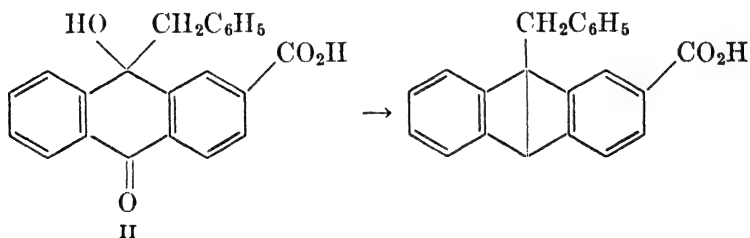
In attempting to account for the unsaturated, olefinic character of the 9,10-double bond, Fries⁹⁷ suggested that the other two double bonds of the central ring are shared unequally with the terminal benzenoid nuclei and are claimed principally by these rings, leaving the double bond at the 9,10-position in a comparatively isolated or imperfectly conjugated condition. This idea can be expressed in some measure in a formula by using a pair of lines of unequal length to represent the double bond and by placing the shorter of the two lines on the side of the ring recognized as having the greater stability. There is another way of viewing the situation which seems somewhat more concrete. That the central nucleus possesses a rather low order of aromaticity means that the dihydride structure which it acquires on oxidation, reduction, or halogen addition is characterized by a special stability. That this is the case is attested by the fact that the 9,10-dibromide is capable of independent existence, and a measure of the relative stability of 9,10-dihydrophenanthrene as compared with 1,2-dihydronaphthalene is furnished by a comparison of the potentials of the corresponding quinones (Table I, p. 159). The low potential of 9,10-phenanthrenequinone as compared with β -naphthoquinone indicates a greater stability of the tricyclic quinonoid, or dihydride, structure. This stability may be attributed to the fact that both double bonds of the central, quinonoid or dihydride ring are subject to the deactivating influence of the benzenoid rings of which they are also members. According to this view, the central nucleus of phenanthrene is susceptible to oxidation, reduction, and addition reactions chiefly because a comparatively stable dihydride structure can be produced as a result of such reactions. The situation is such that there must be a considerably greater driving force to the occurrence of such changes than in the case of naphthalene. This accounts for the highly unsaturated character of the 9,10-double bond and for the ease of hydrogenation and of other additions. From the heat effect in the conversion of naphthalene into the 1,2-dihydride (9.4 Cal.) and from the potentials of the quinones corresponding to the dihydrides, it is estimated that the heat of hydrogenation of phenanthrene to the 9,10-dihydride is about 15 Cal., that is, intermediate between the values for naphthalene and for cyclohexene (28.6 Cal.⁴).

Anthracene. Anthracene surpasses even phenanthrene in reactivity as can be seen, for example, from the fact that the linear compound

present in crude phenanthrene from coal tar can be removed by preferential oxidation to the quinone, and from the observation that polynuclear hydrocarbons which contain the ring systems of both anthracene and phenanthrene are generally attacked on oxidation chiefly in the anthracene part of the molecule. The addition of one mole of hydrogen or of halogen to anthracene also proceeds very readily, and the point of attack in all these reactions is at the 9 and 10, or *meso*, positions. In the early attempts to account for this seemingly special character of the hydrocarbon, considerable prominence was given to the view that the reactivity is due to the presence of a *para* bond extending between the *meso* positions, as in I.



Hinsberg¹⁰⁴ was one of the first to present a serious objection to this formulation, and, although his argument was based upon a rather cumbersome analogy with phenazines and quinoxalophenazines, the evidence appears entirely valid. The essence of the argument is that the fusion of an angular benzenoid ring to one of the terminal rings of anthracene decreases the reactivity at the *meso* positions in a manner not comprehensible on the basis of the formulation in question. Furthermore, anthracene does not appear to be symmetrical, as pictured in the formula, for the attachment of a second ring to the opposite side of the molecule does not produce an added effect proportionate to that of the first ring. Evidence on this point is furnished by potentiometric data for the corresponding quinones.¹⁰⁵ A less serious objection was cited by Goudet,¹⁰⁶ who found that the levorotary form of the hydroxyanthrone II gave an optically



inactive compound on reduction, contrary to what would be expected on the basis of the *para* bond structure III.

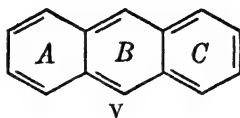
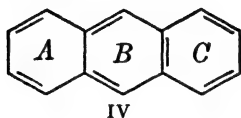
The *para* bond formula was dealt a final blow by the evidence from x-ray analysis (p. 123). All the carbon atoms of anthracene lie in a single

¹⁰⁴ Hinsberg, *Ann.*, **319**, 257 (1901).

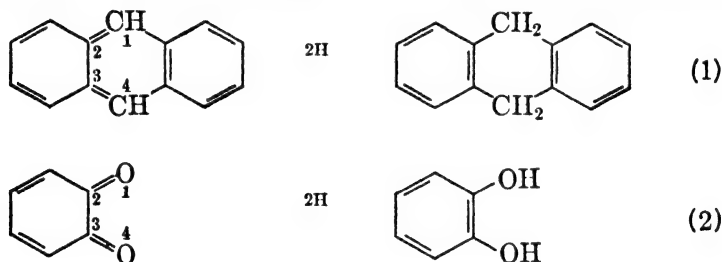
¹⁰⁵ Fieser and Dietz, *J. Am. Chem. Soc.*, **53**, 1128 (1931).

¹⁰⁶ Goudet, *Helv. Chim. Acta*, **14**, 379 (1931).

plane, and consequently the carbon atoms in the *meso* positions are as far removed from one another as the *para* carbon atoms of an isolated benzene ring.¹⁰⁷ According to all available information concerning bond strength, a direct connection between such positions is quite out of the question (p. 125).



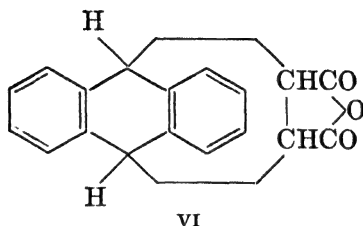
Two Kekulé formulations are possible for anthracene, namely IV and V, and either one may be said to represent the modern counterpart of the *o*-quinonoid formula suggested by Armstrong in 1890. In each formulation at least one ring (A) is present which contains only two double bonds and which, with the ethylenic linkages extending into the central nucleus, constitutes an *o*-quinonoid system of linkages. This arrangement represents a condition less stable than that of a benzenoid ring, and the tendency of the quinonoid nucleus to acquire the benzenoid condition accounts for the reactivity of anthracene. Such a change occurs, for example, as a result of the addition of hydrogen to the 1,4-conjugated system present in the central nucleus (1), a reaction which is analogous to the reduction of *o*-benzoquinone (2). It is understandable that anthra-



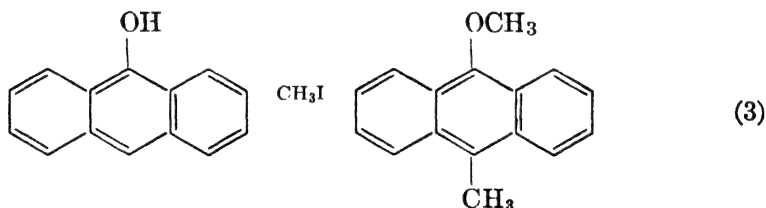
cene is subject to attack at the *meso* positions, and the great driving force in the reduction can be attributed partly to the presence of the reactive *o*-quinonoid system of linkages and partly to the fact that the 9,10-dihydride has a particularly stable structure, for the double bonds are all contained in two isolated benzenoid rings, as in 9,10-dihydrophe-nanthrene. Probably the 9,10-dihydro derivatives of anthracene and phenanthrene do not differ greatly in stability (or in their heats of combustion), and, consequently, the observation⁹⁷ that the heat of combustion of anthracene is greater than that of the angular isomer by 7.0 Cal. affords an approximate indication of the magnitude of the energy content of the anthracene molecule which is attributable solely to the *o*-quinonoid system of linkages.

¹⁰⁷ Meyer, *Z. angew. Chem.*, **41**, 935 (1928).

Other reactions involving a conversion to 9,10-dihydroanthracene derivatives include oxidation, the formation of the 9,10-dibromide, and the Diels-Alder reaction (p. 685) of anthracene with maleic anhydride¹⁰⁸ or with quinone.¹⁰⁹ The ability of the hydrocarbon to yield addition products of the type of VI is particularly illuminating, because of the specificity of the reaction to active diene systems (p. 667), and because



naphthalene and phenanthrene do not form similar products. Endo-anthracene maleic anhydride (VI) is produced by heating the components in boiling xylene solution, and the occurrence of a (reversible) reaction with this and other unsaturated anhydrides, as well as with crotonic acid and acetylene dicarboxylic ester, affords a good indication of the presence of a reactive diene system in the central nucleus. Another indication in the same direction is the C-alkylation of anthranol (3),



observed by K. H. Meyer and Schlösser¹¹⁰ to occur along with O-alkylation when an alkyl halide (but not a sulfate) is employed. The comparatively high degree of unsaturation of anthracene is indicated by the ready reaction with sodium¹¹¹ and in the spectrochemical properties¹¹² of anthracene derivatives, and it has been suggested¹¹³ that the pronounced color of derivatives containing NO₂, OH, NH₂, and Cl finds a satisfactory interpretation in the assumption of a structural relation to true quinones.

¹⁰⁸ Diels and Alder, *Ann.*, **486**, 191 (1931); Clar, *Ber.*, **64**, 2194 (1931).

¹⁰⁹ Clar, *Ber.*, **64**, 1676 (1931).

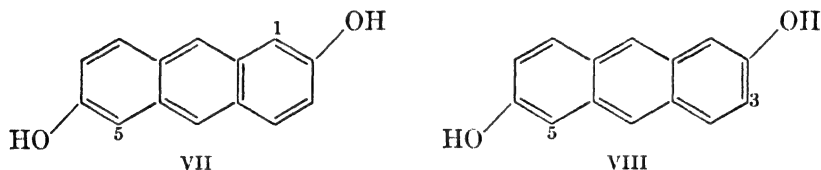
¹¹⁰ Meyer and Schlösser, *Ann.*, **420**, 126 (1920).

¹¹¹ Schlenk, Appenrodt, Michael, and Thal, *Ber.*, **47**, 479 (1914).

¹¹² v. Auwers, *Ber.*, **53**, 941 (1920); v. Auwers and Krollpfeiffer, *Ann.*, **430**, 254 (1923).

¹¹³ Kehrman, *Ber.*, **27**, 3348 (1894); Scholl, *Ber.*, **41**, 2312 (1908).

None of the facts cited thus far provides a means of distinguishing between the alternate *o*-quinonoid formulas IV and V, above. From a consideration of the Fries rule (p. 156), it would appear that the first of these structures is the more likely, because it represents a more stable system. Formula IV contains an *o*-benzoquinonoid ring (A) and two benzenoid rings combined in the form of a normal naphthalene nucleus (BC); in formula V the rings A and B constitute a highly reactive and unstable 2,3-naphthoquinonoid unit, and there is only one benzenoid ring (C). As Fries⁹⁷ stated the case, there is in the first instance a closer average approach to the stable condition of the isolated benzene ring, and consequently IV is the preferred structure. Fries sought to test this prediction by studying the bromination of 2,6-dihydroxyanthracene. If the structure is that of VII, the bromine atoms should be directed to the two enolic *ortho* positions 1 and 5, whereas the alternate structure VIII

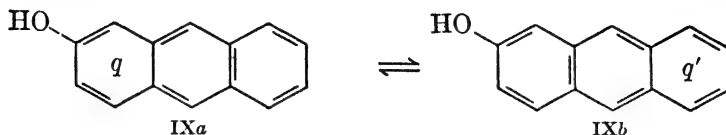


should lead to 3,5-substitution. It was found that bromination occurs at the 1- and 5-positions, as predicted for a compound of the formula VII, but the observation does not exclude the possibility that solutions of the substance contain appreciable quantities of both forms and that VII is merely the more abundant, or the more reactive, of the two. In extending this work, Fieser and Lothrop¹¹⁴ applied a more rigorous test. The 1- and 5-positions were blocked with alkyl substituents, and the 1,5-dialkyl-2,6-dihydroxyanthracenes were investigated for their ability to couple with diazotized amines. As the tests were entirely negative, it was concluded that the bonds are fixed in the positions indicated in formula VII and that the tautomer corresponding to VIII is not present in any appreciable quantity, for it should give rise to substitution at the 3-position.

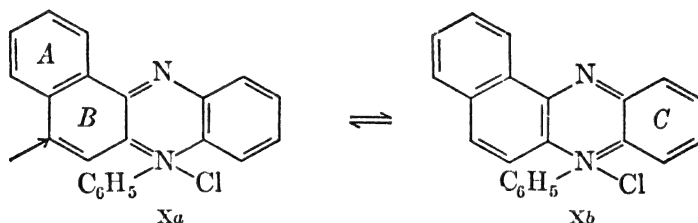
The evidence thus supports the formulation deduced from theoretical considerations, and it indicates a rigidity of the bond structure comparable with that in naphthalene and phenanthrene. With an unsymmetrically substituted compound, such as β -anthrol, it is necessary to account for the fact that the substance has been isolated in only one form, though two structures, IXa and IXb, are theoretically possible. Fries⁹⁷ noted that the change from one structure to the other can be accomplished by a progression of the bonds in the central nucleus, with-

¹¹⁴ Fieser and Lothrop, *J. Am. Chem. Soc.*, **58**, 749 (1936).

out disturbance of the double bonds in the α, β -positions of the terminal rings, and this idea seems in keeping with the nature of the bond fixation indicated by the above experiments. Fieser and Lothrop suggested that the two forms are to be regarded as tautomers, and that an indication



of the position of the equilibrium can be gained by the application of a principle expounded by Kehrman¹¹⁵ in a brilliant paper dealing with the question of the bond structures of azine derivatives. Phenyl-naphthophenazonium chloride, for which two tautomeric forms, Xa and Xb, are possible, is typical. The form Xa contains a naphthoquinonoid



grouping (AB), while Xb has an *o*-benzoquinonoid structure (ring C), and Kehrman reasoned that, since β -naphthoquinone is more stable to reduction than *o*-benzoquinone, Xa should be the predominant tautomer. Evidence in support of this deduction was found in the observation that the compound adds ammonia in alcoholic solution to yield an amino derivative having the substituent in ring B (arrow). The phenazonium salts enter into addition reactions characteristic of the quinones, and they share with these substances the property of forming electromotively active oxido-reduction systems. Kehrman's theory of the factors governing tautomerism among such compounds was placed upon a quantitative basis in later potentiometric studies.¹¹⁶ The equilibrium constant, K , of a pair of tautomers having the normal potentials E_0^α and E_0^β (where the β -form has the higher potential) is given by the expression: $\log K^{25^\circ} = (E_0^\beta - E_0^\alpha)/0.02956$.

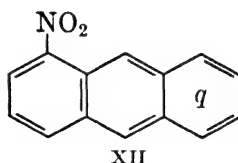
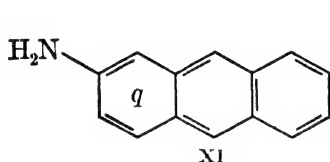
Although reversible oxidation-reduction is not observed with compounds such as anthracene in which the quinonoid system of linkages terminates in carbon, rather than in oxygen or nitrogen, the qualitative application of the established principle seems admissible. In respect to β -anthrol (IX, above), a rational inference concerning the relative sta-

¹¹⁵ Kehrman, *Ber.*, **31**, 977 (1898).

¹¹⁶ Fieser, *J. Am. Chem. Soc.*, **50**, 439 (1928); Fieser and Fieser, *ibid.*, **56**, 1565 (1934)

bility of the two forms can be made from the fact that the oxido-reduction potential of a given hydroxyquinone is considerably lower than that of the corresponding unsubstituted quinone (p. 1038). The hydroxyquinonoid grouping (q) of IXa consequently must represent a condition of greater thermodynamic stability than the unsubstituted quinonoid nucleus (q') of IXb, and the first formula probably corresponds to the structure of the predominant tautomer in solution. The less stable tautomer IXb is probably present in solution in small amounts. (Compare the still unisolated tautomer of 2-hydroxy-1,4-naphthoquinone.)

Alkyl groups influence quinone potentials in the same direction as hydroxyl groups but to only about half the extent, and consequently the less stable forms of 1- and 2-alkylantracenes probably are present in the equilibrium mixtures in somewhat larger amounts. The amino group is considerably more potent than hydroxyl, and β -anthramine must exist very largely in the aminoquinonoid form XI. That the substance is a very weak base and resists diazotization,¹¹⁷ except under special condi-



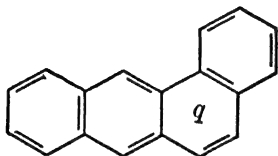
tions,⁹⁷ is easily understood on the basis of this structure, for aminoquinones exhibit similar properties. Highly unsaturated groups, and to a lesser extent halogen atoms, can be expected to shift the equilibrium in the other direction, the more stable form of a compound such as 1-nitroanthracene probably being that in which the substituent is located in the benzenoid ring (XII).

The general theory accounts well for the properties of the higher benzologs of anthracene. It was mentioned above that a benzene ring fused to the molecule in an angular position decreases the reactivity at the *meso* positions, and it is equally true that a linear ring has the opposite effect. A clear demonstration of both relationships is afforded by Clar's¹¹⁸ work on the ease of reaction of the hydrocarbons with maleic anhydride. 1,2-Benzanthracene would be expected to have the β -naphthoquinonoid structure XIII, rather than the alternate *o*-benzoquinonoid structure, and the added ring serves to stabilize the original quinonoid system (q) and hence to decrease the reactivity at the terminal (*meso*) positions of the unsaturated system. An additional benzenoid ring attached

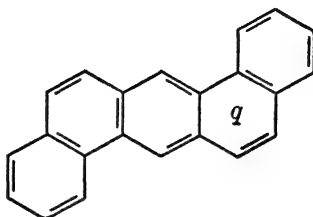
¹¹⁷ Bollert, *Ber.*, **16**, 1635 (1883); Bamberger and Hoffmann, *Ber.*, **26**, 3068 (1893). See also Schroeter, *Ber.*, **57**, 2003 (1924).

¹¹⁸ Clar, *Ber.*, **64**, 2194 (1931); **65**, 503 (1932); Clar and Lombardi, *Ber.*, **65**, 1411 (1932)

at the 5,6-position (XIV) should have little added influence, for it is not in immediate connection with the quinonoid unit. There are indications that this expectation is realized.¹⁰⁵ The situation is quite different when a

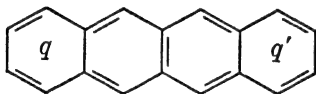


XIII

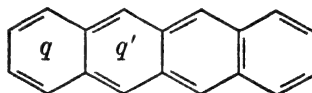


XIV

benzene ring is fused to anthracene in a linear position. The formulas XVa and XVb for naphthacene both represent systems of greater unsaturation and reactivity than anthracene, because in each case two of the four rings are quinonoid (*q*) in character. In XVa two terminal *o*-benzoquinonoid rings are separated by the normal naphthalene unit formed



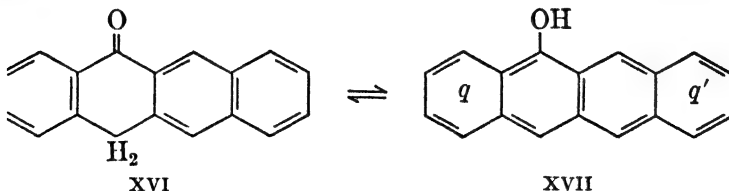
XVa



XVb

by the two central rings, and, although the added quinonoid ring should render the structure more reactive than anthracene, the system at least has greater stability than XVb, where the non-benzenoid rings *q* and *q'* are combined in the form of a 2,3-naphthoquinonoid unit. That such a group would be highly unstable and reactive can be inferred from the non-existence of 2,3-naphthoquinone itself, and from the observation that quinones in which the quinonoid system of linkages extends into two nuclei are characterized by having unusually high reduction potentials (see diphenoquinone, 2,6-naphthoquinone, Table I, p. 159). Formula XVa therefore represents the preferred structure.

The reactivity of naphthacene as compared with anthracene is well illustrated by the properties of its derivatives.¹¹⁹ The equilibrium be-



XVI

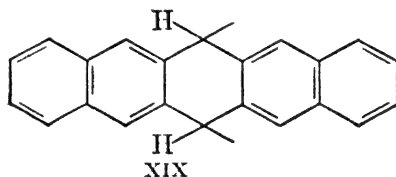
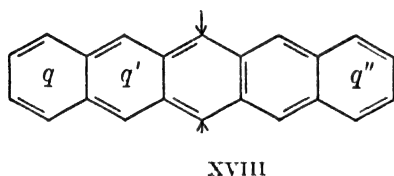
XVII

tween 2,3-benz-9-anthrone (XVI) and the anthranol-form XVII so greatly favors the keto form that the substance, unlike anthranol itself,

¹¹⁹ Fieser, *J. Am. Chem. Soc.*, **53**, 2329 (1931).

fails to dissolve in alkali. The anthranol acetate is formed ¹²⁰ much less readily ¹¹⁹ than usual, and the anthranol is very easily reduced to an unusually stable dihydride. The observations all reveal a pronounced tendency of the doubly quinonoid structure to revert to the more stable condition of the 9,10-dihydride. The striking observation that crystalline naphthacenequinone does not give the usual vat test with alkaline hydrosulfite is similarly attributable to the lack of stability of the hydroquinone.

Still greater reactivity is displayed by Clar's ¹²¹ *lin.*-dibenzanthracene, a hydrocarbon of particular interest because of its blue color. No very stable arrangement of the double bonds of this compound is possible, and the best adjustment that can be achieved is represented in formula XVIII. This structure includes a 2,3-naphthoquinonoid unit (qq') at one end of the molecule and an *o*-benzoquinonoid nucleus (q'') at the other, and consequently the high degree of unsaturation of the hydrocarbon, as manifested in its reactivity and color, is easily understandable. Reagents would be expected to attack the substance in the central ring, for these positions are at the ends of the more reactive 2,3-naphthoquinonoid system, and this expectation is realized. Clar took a different view of the situation and postulated for the hydrocarbon the biradical (p. 602) formula XIX. He suggested that anthracene itself and the



other aromatic compounds exist to some extent in a diyl phase, but that the pentacyclic hydrocarbon has a complete biradical character.¹²² These speculations, although subject to much adverse criticism,¹²³ have continued to attract attention.¹²⁴ In an attempt to settle the matter, E. Müller ¹²⁵ investigated the magnetic susceptibility of the blue hydrocarbon and found that the compound does not exhibit paramagnetism, as univalent radicals and one authentic biradical were found to do. He concluded that the amount of diyl, if present, cannot exceed 1 per cent.

¹²⁰ Barnett and Lowry, *Ber.*, **65**, 1649 (1932).

¹²¹ Clar and John, *Ber.*, **62**, 3021 (1929); **63**, 2967 (1930).

¹²² Clar, *Ber.*, **65**, 503 (1932); **66**, 202 (1933); **69**, 607, 1671 (1936).

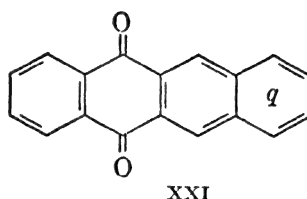
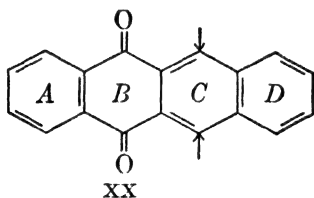
¹²³ Scholl and Böttger, *Ber.*, **63**, 2133 (1930); Scholl and Meyer, *Ber.*, **67**, 1229, 1236 (1934); Conrad-Billroth, *Ber.*, **66**, 639 (1933).

¹²⁴ Kon, *Ann. Repts. Chem. Soc. (London)*, **29**, 163-171 (1932).

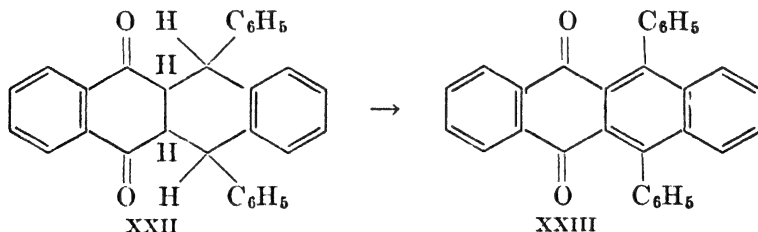
¹²⁵ Müller and Müller-Rodloff, *Ann.*, **517**, 134 (1935); Müller and Bunge, *Ber.*, **69**, 2164 (1936).

Although it is conceivable that a fixed opposition of the electron spins in a biradical could eliminate the paramagnetic effect, such an explanation seems improbable. The evidence available does not warrant acceptance of the diyl formula as representing anything more, perhaps, than a reaction phase, and the general theory of aromatic structures based upon a rational extension of the concept of the Kekulé ring seems to provide an adequate interpretation of the facts without this added assumption.

The principles defining the bond structures of the polynuclear aromatic hydrocarbons seem to apply also to the quinones and hydro deriva-



tives of these substances. On the basis of the Fries rule, it was predicted^{97, 126} that naphthacenequinone has the structure XX rather than XXI, for in XX the rings C and D are benzenoid and constitute a normal naphthalene system, while in XXI the terminal ring is quinonoid and forms a part of a unit corresponding to the unstable form of naphthalene. Allen and L. Gilman¹²⁷ found support for this view in the observation that phenylmagnesium bromide adds to the two 1,4-conjugated systems formed by the nuclear double bonds in ring C with the carbonyl groups, giving two stereoisomeric products of the structure XXII. Air oxidation in alkaline solution of the enolized material gave XXIII. The behavior is quite different from that of anthraquinone and phenanthrenequinone, with which Grignard reagents give exclusively carbinols, and it is inferred that in these compounds a 1,4-system is not available, the bonds of anthraquinone being arranged as in ring A of XX. The unusual arrange-

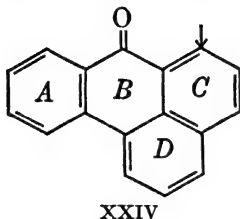


ment of bonds in the oxygenated ring (B) of naphthacenequinone may modify slightly the character of this ring, but it seems unlikely that true quinone characteristics are entirely lost. 1,4-Anthraquinone probably

¹²⁶ Fieser and Martin, *J. Am. Chem. Soc.*, **57**, 1844 (1935).

¹²⁷ Allen and Gilman, *ibid.*, **58**, 937 (1936).

has a similar bond structure,¹²⁸ and it undergoes reversible reduction and exhibits other usual properties of quinones. The 1,4-addition of the Grignard reagent (p. 672) has been observed also in benzanthrone, XXIV, the aryl or alkyl group appearing at the 4-position (arrow).¹²⁹



The observation locates one double bond in ring C, and from the principle of greatest stability it seems likely that the remainder of the bonds in rings C and D are arranged as in naphthalene.¹³⁰

Pyrene. This tetracyclic hydrocarbon presents an interesting combination of fused rings embodying groupings of the naphthalene, phenanthrene, and diphenyl types. In the degree of reactivity to substituting agents, pyrene is roughly comparable with anthracene. In an extensive study of the hydrocarbon, Vollmann, Becker, Corell, and Streeck¹³¹ found that monosubstitution occurs solely at the 3-position, which corresponds to one of the chief, if by no means exclusive, points of attack in phenanthrene. A second substituent is introduced about as easily as the first and invariably enters the second *peri*-ring at the 8- or 10-position, giving a mixture of 3,8- and 3,10-isomers in which the latter predominates. In contrast to the point of attack in substitutions, the addition of ozone occurs at the 1,2- and 6,7-positions. These results are interpreted¹³² to indicate that in its most stable state pyrene has the 1,4-naphthoquinonoid¹³³ bond structure I. Predominant disubstitution at the 3,10-positions is considered to occur at the ends of the active quinonoid system of linkages (arrows). The formation of 3,8-derivatives may occur through the possibly more reactive but considerably less abundant 1,5-naphthoquinonoid form II. The change from one bond isomer to the other would involve merely a progression of the bonds in the upper terminal ring. A greater stability for I as compared with II is consistent with the Fries rule, for the former structure contains three benzenoid rings (*b*) while the latter contains but two.

¹²⁸ Fieser, *ibid.*, **50**, 465 (1928).

¹²⁹ Charrier and Ghigi, *Gazz. chim. ital.*, **62**, 928 (1932); *Ber.*, **69**, 2211 (1936); Allen and Overbaugh, *J. Am. Chem. Soc.*, **57**, 740, 1322 (1935).

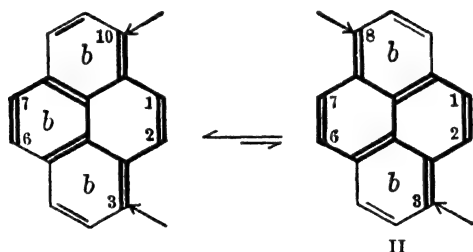
¹³⁰ See, however, Clar, *Ber.*, **65**, 846 (1932).

¹³¹ Vollmann, Becker, Corell, and Streeck, *Ann.*, **531**, 1 (1937).

¹³² Fieser and Seligman, *J. Am. Chem. Soc.*, **60**, 170 (1938).

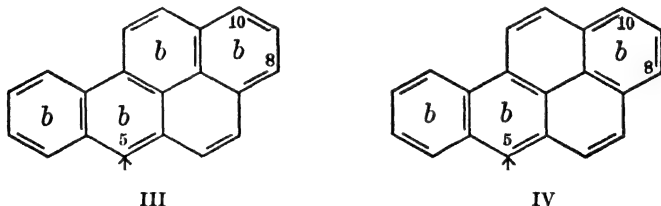
¹³³ Clar, *Ber.*, **65**, 1426 (1932).

The fact that 3-hydroxypyrene fails to couple with diazotized amines indicates a rigidity of the bond structure in at least a part of the molecule and shows that the 3- and 5-positions are not identical, as they would appear to be from the outline formula. The structure I with a hydroxyl group at the 3-position and a single bond connecting positions 3 and 4 evidently is more stable than that with the substituent at position 5. The explanation may be that the hydroxyl group, which is known to have a stabilizing (potential-lowering) effect on true quinones, is joined directly to the quinonoid system in the former, but not the latter, case. That neither 3,10- nor 3,8-dihydroxypyrene can be caused to couple with diazotized *p*-nitroaniline indicates that the two dihydroxy compounds have the alternate bond structures I and II, respectively. This must



mean that the influence of the attachment of a hydroxyl group to a quinonoid system is so pronounced that two such substituents in the 3- and 8-positions can effect the stabilization of the otherwise more reactive 1,5-naphthoquinonoid system of II.

3,4-Benzpyrene. If pyrene tends to exist chiefly in the 1,4-naphthoquinonoid form (I, above), the most probable bond structure for 3,4-benzpyrene is that shown in formula III, in which the four benzenoid rings constitute a chrysene unit. The alternate formulation IV, derived



from the 1,5-naphthoquinonoid form of pyrene (II), represents the hydrocarbon as a 1,2-benzanthracene derivative containing but three benzenoid rings. The evidence available does not distinguish between the two structures, and the fact that the hydrocarbon suffers oxidation at positions 5, 8, and 10 perhaps is indicative of attack at the exposed ends of the 1,4- and 1,5-naphthoquinonoid systems of the two forms.

3,4-Benzpyrene is of special interest because of the remarkable reactivity which it manifests in substitution reactions.¹³⁴ In susceptibility to substitutions, the substance surpasses all other known unalkylated, fully aromatic hydrocarbons. Oxidation with lead tetraacetate proceeds smoothly at room temperature and affords the 5-acetoxy derivative in over 90 per cent yield, and the reaction with methylformanilide to give the 5-aldehyde proceeds equally well. The hydrocarbon even couples with diazotized *p*-nitroaniline in acetic acid (5-position), and thereby exhibits nuclear reactivity comparable with that of a phenol or amine. The exclusive point of attack, except in the (hindered) Friedel and Crafts reaction, is at position 5. This is at one end of a quinonoid system of linkages, and it is also a *meso* position, flanked by activating rings on either side.

Of possible significance to the theory of aromatic substitutions is the fact that 3,4-benzpyrene exhibits no tendency to form addition products. In contrast to the situation in the naphthalene, phenanthrene, and anthracene series, no reaction products of dihydride structure have been encountered, and reactions which can proceed only by an addition do not appear to take place. In sharp contrast to the behavior of anthracene and 1,2-benzanthracene, 3,4-benzpyrene fails to add maleic anhydride (citation¹³⁴ from Bachmann). The facile substitutions of the hydrocarbon therefore appear to be independent of any process of addition. Among other polynuclear hydrocarbons, there is a sufficient, if perhaps entirely fortuitous, parallelism between reactivity in substitutions and in additions to invite the speculation that the substitutions may proceed by way of addition mechanisms. The case of 3,4-benzpyrene, however, demonstrates that the two processes can be entirely distinct and uncorrelated.

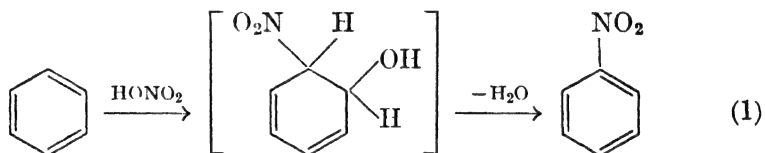
THE NATURE OF AROMATIC SUBSTITUTIONS

The question of the mechanism of aromatic substitutions is a complicated one, for there is considerable variety in the types of reactions and in the nature of the compounds undergoing substitution. It is an open question whether different substituting agents act upon a given compound in the same way, and whether a given type of substitution follows the same general course in the benzene series as with polynuclear hydrocarbons. The course of the reaction conceivably may vary also with the nature of the directing groups. There may well be more than one path by which a substituent can enter an aromatic nucleus, and cer-

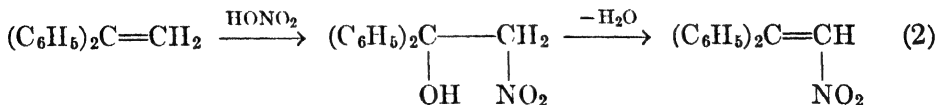
¹³⁴ Fieser and Campbell, *J. Am. Chem. Soc.*, **60**, 1142 (1938) · Fieser and Hershberg, *ibid.*, **60**, 2542 (1938); **61**, 1565 (1939).

tainly caution should be exercised in reasoning by analogy unless a secure correspondence can be established between the cases in question.

Nitration and Sulfonation. Shortly after proposing the cyclohexatriene formula for benzene, Kekulé¹³⁵ attempted to determine the course of the reaction between nitric acid and ethylene in order to make a comparison with the aromatic nitration reaction. Difficulties were encountered, however, and not much progress was made. The reaction affords mainly products of oxidation, but Wieland and Sakellarios,¹³⁶ by using a mixture of nitric and fuming sulfuric acids, succeeded in isolating small amounts of β -nitroethyl nitrate, $\text{CH}_2(\text{NO}_2)\text{CH}_2\text{ONO}_2$. This was thought to result from the esterification of $\text{CH}_2(\text{NO}_2)\text{CH}_2\text{OH}$, formed as a primary product of addition. It was found further that β -nitroethyl alcohol, prepared¹³⁷ in another way, yields the nitric ester with nitric acid, and can be dehydrated to nitroethylene with the use of phosphorus pentoxide, and consequently it appeared that nitric acid adds to ethylene as $\text{HO}-\text{NO}_2$ and that a substitution product can be produced by the elimination of water from the addition product. The observations were regarded as affording an analogy for the hypothesis that the nitration of benzene proceeds by an addition-elimination mechanism (1).



A still closer analogy was reported by Anschütz and Hilbert,¹³⁸ who studied the nitration of α,α -diphenylethylene in glacial acetic acid. Under mild conditions of operation a nitro alcohol was obtained, and this yielded the corresponding unsaturated nitro compound on warming a solution of the substance in glacial acetic acid containing a trace of nitric acid. The complete process (2) corresponds to that postulated for the aromatic substitution. Unsaturated nitro compounds have been ob-



tained also in small amounts from certain alkenes by the action of nitric acid alone or in carbon tetrachloride solution, isobutylene giving $(\text{CH}_3)_2\text{C}$

¹³⁵ Kekulé, *Ber.*, **2**, 329 (1869).

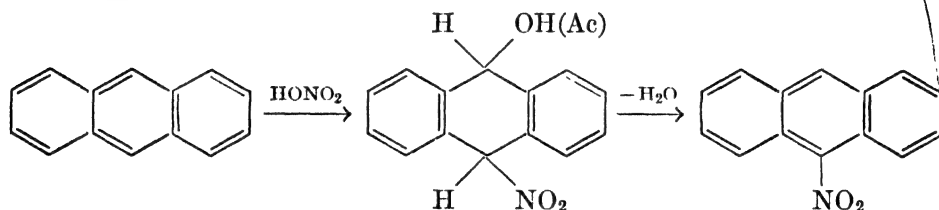
¹³⁶ Wieland and Sakellarios, *Ber.*, **53**, 201 (1920).

¹³⁷ Wieland and Sakellarios, *Ber.*, **52**, 898 (1919).

¹³⁸ Anschütz and Hilbert, *Ber.*, **54**, 1854 (1921).

$=\text{CHNO}_2$,¹³⁹ and isoamylcne yielding $(\text{CH}_3)_2\text{C}=\text{C}(\text{NO}_2)\text{CH}_3$.^{139, 140} A particularly interesting case is that of ethyl *p*-nitrocinnamate, which yields $\text{O}_2\text{NC}_6\text{H}_4\text{CH}=\text{C}(\text{NO}_2)\text{CO}_2\text{C}_2\text{H}_5$ on treatment with nitric and sulfuric acid at room temperature,¹⁴¹ that is, under the conditions of an ordinary aromatic nitration.

It can be argued that the postulated dihydrobenzenoid intermediate would be so unstable under the dehydrating action of the strong acid or mixed acid required to produce it that it might well elude isolation. Furthermore, analogous products have been isolated from certain cyclic compounds of less pronounced aromaticity than benzene. By the action of nitric acid on anthracene in glacial acetic acid, Meisenheimer and Connerade¹⁴² obtained a solution of nitrodihydroanthranol (or its ace-



tate), and a conversion to 9-nitroanthracene was brought about by treatment with mineral acids. A substance similarly regarded as a product of 1,4-addition has been obtained as the acetate from furan.¹⁴³ Though these substances may correspond to an essential step in the typical nitration of benzene, it is also possible that the addition compounds are formed in independent reactions not connected with substitution. The existence of an addition compound in the case of anthracene is understandable in either event, for the great reactivity of this hydrocarbon enables a reaction to occur under mild conditions, and the special structure of a 9,10-dihydroanthracene derivative confers upon it unusual stability. These factors would favor equally the formation of an intermediate essential to the nitration, or a by-product, and experimental evidence upon which to base a decision is not available.

It seems necessary to view the analogy between benzene and anthracene or furan in the nitration reaction with caution, and Michael and Carlson¹⁴⁴ have attacked the experimental basis for the analogy with the supposed addition of nitric acid to alkenes. These investigators found that at a low temperature colorless nitric acid containing no nitrous

¹³⁹ Haitinger, *Ann.*, **193**, 366 (1878).

¹⁴⁰ Wieland and Rahn, *Ber.*, **54**, 1770 (1921).

¹⁴¹ Friedlaender and Mähly, *Ber.*, **16**, 848 (1883); Friedländer, *Ann.*, **229**, 203 (1885)

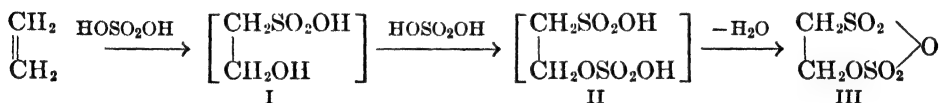
¹⁴² Meisenheimer and Connerade, *Ann.*, **330**, 133 (1904).

¹⁴³ Freure and Johnson, *J. Am. Chem. Soc.*, **53**, 1142 (1931).

¹⁴⁴ Michael and Carlson, *ibid.*, **57**, 1268 (1935).

oxides does not add to ethylene but attacks it destructively, and that it merely polymerizes α,α -diphenylethylene. The pure acid in carbon tetrachloride solution at -20° was found to add as $\text{H}-\text{ONO}_2$ to isobutylene and to isoamylene, giving the esters $(\text{CH}_3)_2\text{C}(\text{ONO}_2)\text{CH}_3$ and $(\text{CH}_3)_2\text{C}(\text{ONO}_2)\text{CH}_2\text{CH}_3$. Michael and Carlson consider it probable that the products obtained by previous investigators with ordinary nitric acid are formed indirectly by interaction with nitrous gases produced in oxidative side reactions, and that the product $\text{CH}_2(\text{NO}_2)\text{CH}_2\text{ONO}_2$ obtained by Wieland and Sakellarios with a mixture of nitric and fuming sulfuric acids is produced by the addition to ethylene of the mixed anhydride, $\text{O}_2\text{N}-\text{OSO}_3\text{H}$, giving $\text{CH}_2(\text{NO}_2)\text{CH}_2\text{OSO}_3\text{H}$, followed by replacement of SO_3H by NO_2 .

The processes of sulfonation and nitration are clearly related, and Wieland¹³⁶ interpreted the former reaction as proceeding through the addition of $\text{HO}-\text{SO}_2\text{OH}$ to a double bond of the benzene ring with subsequent dehydration. That sulfuric acid can on occasion add to an alkene in this manner, rather than function as $\text{H}-\text{OSO}_2\text{OH}$, as usual, Wieland inferred from the fact that ethylene yields carbyl sulfate (III) rather than ethyl sulfuric acid, on reaction with fuming sulfuric acid. It was assumed that an addition of $\text{HO}-\text{SO}_2\text{OH}$ to give isethionic acid (I) is followed by esterification to ethionic acid (II), and dehydration to



III. Michael and Weiner,¹⁴⁵ however, pointed out that the suggested mechanism does not attribute any function to the SO_3 , S_2O_6 , or $\text{H}_2\text{S}_2\text{O}_7$ present in fuming sulfuric acid, whereas carbyl sulfate is formed only when such acid is used. From a semi-quantitative study of the reaction, these investigators concluded that the essential reaction is between ethylene and pyrosulfuric acid, and that this adds not as an acid but as an anhydride, giving ethionic acid (II) directly.



When sulfuric anhydride is in excess, this reacts with II to form carbyl sulfate.

Michael's work indicates that nitric acid and sulfuric acid do not add to ethylene as $\text{HO}-\text{NO}_2$ and $\text{HO}-\text{SO}_2\text{OH}$, and consequently that there is no analogy in the chemistry of simple alkenes to support the addition-elimination theory of the aromatic substitutions. It may be

¹⁴⁵ Michael and Weiner, *ibid.*, **58**, 294 (1936).

remarked, however, that a comparison of benzene with ethylene is perhaps of doubtful value. That the acids function as $\text{H}-\text{ONO}_2$ and $\text{H}-\text{OSO}_2\text{OH}$ with ethylene hardly provides a useful clue to the course of the reactions with benzene, for similar additions are out of the question in the latter case. The reaction $-\text{CH}=\text{CH}- + \text{H}-\text{OSO}_3\text{H} \rightleftharpoons -\text{CH}_2\text{CH}(\text{OSO}_3\text{H})-$ is reversible even with alkenes, and, since a dihydro-benzenoid addition product of this type could stabilize itself only by reverting to the components, it is clear that in the aromatic series the equilibrium must represent a condition amounting practically to non-addition; addition in this manner probably has no significance except, perhaps, in promoting a deuterium exchange. With this mode of reaction blocked, the acids in question evidently act upon benzene in some other way, and the addition hypothesis represents one possibility. It is also possible that substitution involves merely a direct metathesis, $\text{C}_6\text{H}_5 \text{ [H + HO] NO}_2$. Substitutions of this type apparently occur in the nitration of alkanes ^{146, 147} with dilute nitric acid and in the nitration of toluene in the side chain ¹⁴⁶ under similar conditions.

As an alternative mechanism, Michael suggested that nitration and sulfonation may involve the addition of a nuclear hydrogen atom and the aromatic residue to an unsaturated oxygen of the acid and the attached nitrogen or sulfur, respectively. Water is then assumed to separate from the addition product, the complete process being as follows: $\text{C}_6\text{H}_5\text{H} + \text{NO}_2(\text{OH}) \rightarrow [\text{C}_6\text{H}_5\text{NO}(\text{OH})_2] \rightarrow \text{C}_6\text{H}_5\text{NO}_2 + \text{H}_2\text{O}$. It is assumed that benzenesulfonic acid can result from an addition of benzene to sulfuric acid, SO_3 , or S_2O_6 , and that the diphenyl sulfone formed in the reaction with fuming sulfuric acid arises by an addition of two molecules of benzene to S_2O_6 . While this mode of addition represents a possible course for at least some aromatic substitutions, the theory has no firmer foundation in experimental evidence or analogy than the others. The mechanism suggested for the sulfonation process seems questionable, for two centers of unsaturation present in sulfuric acid are both semi-polar (p. 1827) double bonds, and it is doubtful whether they are amenable to additions comparable with additions to $\text{C}=\text{O}$ or $\text{C}=\text{C}$. The addition product would have an electronic structure characterized by a shell of twelve electrons surrounding sulfur, and such a structure seems subject to question.

No very satisfactory conclusion can be drawn from this survey of two characteristic substitution reactions, for it appears that the mechanism of the processes is still an open question awaiting further experimental investigation.

¹⁴⁶ Konowalow, *Ber.*, **23**, 1852 (1895).

¹⁴⁷ Markownikoff, *Ann.*, **302**, 15 (1898).

Halogenation and the Friedel-Crafts Reaction (p. 553). The idea that the catalyzed bromination of benzene may proceed through an addition to the unsaturated nucleus and an elimination of hydrogen bromide was suggested by Armstrong¹⁴⁸ at an early date, and a number of observations have accumulated which seem to support the hypothesis. Abundant analogy can be found in the aliphatic series for the 1,2- or 1,4- addition of bromine, and there are substitutions which seem to occur by an addition-elimination mechanism. α,α -Diphenylethylene¹⁴⁹ and triphenylethylene,¹⁵⁰ for example, yield substitution products on bromination at a somewhat elevated temperature, and an intermediate addition product is sufficiently stable to be isolated only in the case of the latter hydrocarbon. Furthermore, definite and well-characterized halogen-addition products are known in the aromatic series. Phenanthrene reacts with bromine in carbon disulfide in the cold to give the crystalline 9,10-dibromide, and this decomposes on being heated with the formation of 9-bromophenanthrene and hydrogen bromide. Anthracene adds bromine at a temperature well below zero, and the 9,10-dibromide decomposes at room temperature. Somewhat more stable dibromides of α -haloanthracenes have been prepared,¹⁵¹ and anthracene dichloride has been well characterized.¹⁵² The isolation of a similar addition product in the furan series is reported by Gilman and Wright.¹⁵³ Benzene itself forms addition products with chlorine and bromine, although in this case three molecules of halogen invariably are absorbed and intermediate products are unknown.* Ferric bromide, and other metal halides and halogen carriers, promote the formation of bromobenzene, but in the absence of such catalysts benzene is converted into the hexabromide, the addition reaction proceeding particularly rapidly in the sunlight.

It would appear possible on the basis of the foregoing observations that in any case benzene and bromine first combine, probably reversibly, to form a 1,2-(or 1,4-) dibromide, and that the fate of this unsaturated intermediate is determined by the presence or absence of a catalyst of the specific type favoring substitution. Without such a catalyst the unsaturated intermediate rapidly absorbs two additional moles of bromine, but if ferric bromide or a similar substance is present this catalyzes

¹⁴⁸ Armstrong, *J. Chem. Soc.*, **51**, 258 (1887).

¹⁴⁹ Hepp, *Ber.*, **7**, 1409 (1874).

¹⁵⁰ Hell and Wiegandt, *Ber.*, **37**, 1431 (1904); Klages and Heilmann, *Ber.*, **37**, 1455 (1904).

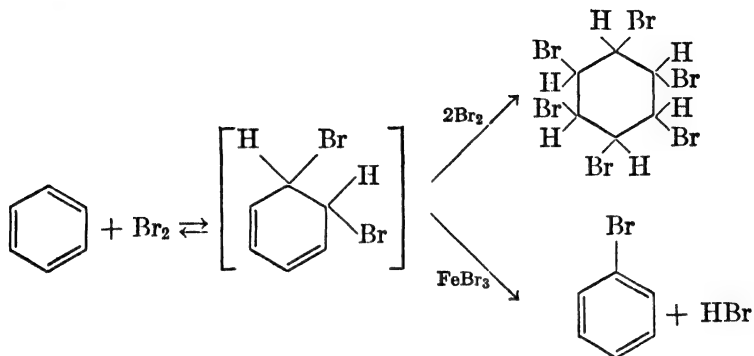
¹⁵¹ Barnett and Cook, *J. Chem. Soc.*, **125**, 1084 (1924); Barnett and Mathews, *Rec. trav. chim.*, **43**, 530 (1924).

¹⁵² Meyer and Zahn, *Ann.*, **396**, 171 (1913).

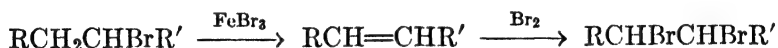
¹⁵³ Gilman and Wright, *J. Am. Chem. Soc.*, **52**, 3349 (1930).

* For references to work on mixed halides, see van der Linden, *Rec. trav. chim.*, **55**, 282 (1936).

the elimination of hydrogen bromide and a stable substitution product results. There are some indications in the chemistry of aliphatic halogen compounds that metal halides can function in the manner postulated. Gustavson¹⁵⁴ observed that, in the Friedel and Crafts reaction with ben-



zene, *n*-propyl bromide yields isopropylbenzene, and Kekulé¹⁵⁵ showed that this is because the normal halide is converted into the isomeric halide under the influence of the aluminum bromide employed to effect the condensation. Presumably the isomerization is the result of the catalyzed elimination of hydrogen bromide, and re-addition, and Kerez¹⁵⁶ reported that propylene can be obtained on conducting the isomerization at an elevated temperature. Victor Meyer¹⁵⁷ observed that on bromination of aliphatic halides in the presence of ferric chloride or antimony pentachloride the second halogen invariably enters a position adjacent to that occupied by the first, and he considered that the reaction probably proceeds as follows:



The plausibility of the classical addition-elimination theory as applied to bromination has been the subject of much debate, but only recently has the validity of the mechanism been submitted to direct test. The matter hinges on the question of whether a dibromide is a necessary precursor of a given bromo-substitution product, and, although the dibromide of benzene is not available for experimentation, there is no theoretical objection to the use of the crystalline 9,10-dibromides of phenanthrene and anthracene to settle the point at issue. Price¹⁵⁸ under-

¹⁵⁴ See Wagner, *Ber.*, **11**, 1251 (1878).

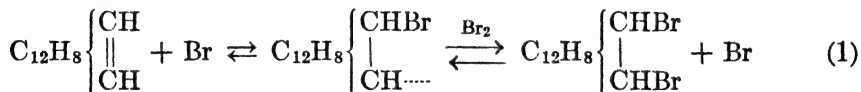
¹⁵⁵ Kekulé and Schrötter, *Ber.*, **12**, 2279 (1879); Gustavson, *Ber.*, **16**, 958 (1883).

¹⁵⁶ Kerez, *Ann.*, **231**, 285 (1885).

¹⁵⁷ Meyer and Müller, *J. prakt. Chem.*, [2] **46**, 182 (1892); Meyer and Petrenko-Kritschenko, *Ber.*, **25**, 3304 (1892).

¹⁵⁸ Price, *J. Am. Chem. Soc.*, **58**, 1834, 2101 (1936); see also, Fieser and Price, *ibid.*, **58**, 1838 (1936).

took an investigation of phenanthrene dibromide with this end in view and found, in the first place, that the addition reaction between phenanthrene and bromine in non-aqueous solvents is reversible and that the position of the equilibrium and the rate of the reaction are measurable by analytical methods ($-\Delta F^{25^\circ} = 3.2$ Cal.). He found further that the addition of bromine is a chain reaction, possibly propagated by free radicals and bromine atoms (1), the evidence being that the reaction is inhibited by substances such as diphenylamine and tetrabromohydroquinone which can donate atoms of hydrogen to combine with bromine atoms and break the chain, reverting thereby to stable compounds (tetra-

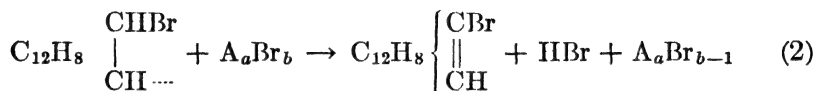


phenylhydrazine, tetrabromoquinone). Estimations of the number of molecules in the chain indicated that the chain length decreases with increasing temperature, which accounts for the absence of a temperature coefficient in the measured reaction. Kharasch, White, and Mayo¹⁵⁹ later showed that the addition is a photochemical, oxygen-catalyzed reaction.

On investigating the influence of various halogenation catalysts, Price observed that aluminum chloride, antimony pentachloride, stannic chloride, iodine, and similar substances promote the substitution reaction, as indicated by the liberation of hydrogen bromide, when added to a solution containing phenanthrene, bromine, and the dibromide. Some of these reagents influence the addition reaction as well, and the effect may be either to accelerate or to retard the addition of bromine. Iodine inhibits the formation of phenanthrene dibromide, probably by interacting with chain-propagating bromine atoms, but it acts as a typical catalyst of the reaction leading to the production of 9-bromophenanthrene and the liberation of hydrogen bromide. The most important point at issue was to determine whether these products arise from the direct decomposition of phenanthrene dibromide or by some other route, and the results supported the latter conclusion. The pure dibromide is stable in solution at 25° and does not revert to the equilibrium mixture containing phenanthrene and bromine unless a trace of free bromine is present. The addition of iodine to a solution of the pure dibromide produces no change, and hydrogen bromide is liberated only after a trace of free bromine has been introduced. The rate of HBr-formation is then no greater than in a solution initially containing equivalent amounts of phenanthrene and bromine. Evidently 9-bromophenanthrene is not

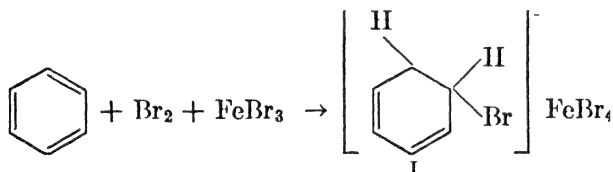
¹⁵⁹ Kharasch, White, and Mayo, *J. Org. Chem.*, **2**, 574 (1938).

produced by the elimination of hydrogen bromide from the addition product, and indeed when phenanthrene dibromide is treated with potassium acetate-hydroxide in methanol solution it yields phenanthrene rather than 9-bromophenanthrene.¹⁶⁰ The addition-elimination theory seems to be definitely excluded by these observations, and it appears that the dibromide is not a necessary precursor of the substitution product but that it probably is formed from a radical or ion. If a radical is

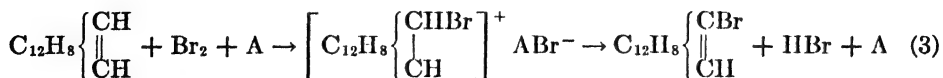


involved in the first phase of the reactions, a catalyst A may function in combination with bromine as a hydrogen acceptor and so influence the rate of substitution (2).

Price notes that the substitution can be interpreted equally well on the assumption that the essential intermediate subject to influence by catalysts is a coördinative complex of a type suggested by Pfeiffer and Wizinger.¹⁶¹ These authors observe that the usual catalysts (FeBr_3 , AlCl_3 , SbCl_5 , SnCl_4 , I_2) are all substances capable of forming complex anions with chlorine or bromine, and they postulate the formation of polar complexes of the type indicated in formula I. It is considered that



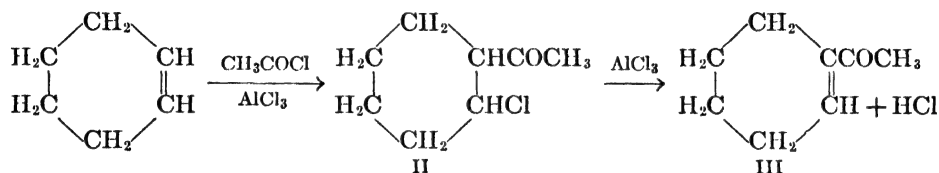
the ionic charge is only weakly developed except when polar groups are present in the ring, and that such groups by repulsion or attraction determine the localization of the charge and hence fix the orientation (see below). The formulation is supported by the isolation of complexes as intermediates in the bromination of α, α -di-(*p*-dimethylaminophenyl)-ethylene, for example, $\{[(\text{CH}_3)_2\text{NC}_6\text{H}_4-]_2\text{C}^+ - \text{CH}_2\text{Br}\} \text{Br}_3^-$. According to this theory, the bromination of phenanthrene follows the course indicated in scheme (3), where A is the catalyst molecule.



¹⁶⁰ Fieser, Jacobsen, and Price, *J. Am. Chem. Soc.*, **58**, 2163 (1936).

¹⁶¹ Pfeiffer and Wizinger, *Ann.*, **461**, 132 (1928). See also Pfeiffer and Schneider, *J. prakt. Chem.*, [2] **129**, 129 (1931); Wizinger, *Z. angew. Chem.*, **44**, 469 (1931); *ibid.*, **46**, 756 (1933); Meerwein, *ibid.*, **38**, 815 (1925).

The conclusions regarding halogenation probably are applicable to the Friedel and Crafts reaction, for there is considerable correspondence in the two processes. Both reactions proceed under the catalytic influence of specific metal halides, and hydrogen halide is a product of both substitutions.¹⁶² In the catalyzed reaction of acid chlorides, there is some analogy in the action of these substances and of bromine on compounds containing isolated double bonds. Darzens¹⁶³ observed an intermediate addition in the reaction of acetyl chloride with cyclohexene, and the chloroketone II was further characterized by Wieland and Bettag.¹⁶⁴



The addition occurs at a temperature of -18° , and, at a somewhat higher temperature, in the presence of aluminum chloride, hydrogen chloride is eliminated and the unsaturated ketone III is produced. The analogy to the addition of bromine to an alkene and to the catalytic decomposition of a bromide is evident. The Darzens reaction has been adapted to synthetic purposes¹⁶⁵ and affords a convenient method of effecting cyclizations. Because of the reactivity of the isolated ethylenic linkage as compared to a benzenoid double bond, the milder condensing agent stannic chloride is usually employed to effect the addition, and hydrogen chloride is eliminated with the use of dimethylaniline.

From a practical point of view, there are important differences in the Friedel and Crafts synthesis of ketones and of alkylated hydrocarbons. In the former case the unsaturated group introduced decreases the reactivity of the nucleus and a sharp stopping point is reached at the stage of monosubstitution, whereas the introduction of an alkyl group facilitates further reaction and some polysubstitution is inevitable. This difference, however, does not alter the theoretical aspects, and the same can be said of the fact that the amount of aluminum chloride required for the reaction with alkyl halides is only a small fraction of that which must be used to effect condensation with an acyl halide or an anhydride. In the typical Friedel and Crafts ketone synthesis both the acid chloride and reaction product form with aluminum chloride complexes which are stable in the anhydrous reaction mixture, and it is necessary to employ at least one

¹⁶² Schaarschmidt, *Z. angew. Chem.*, **37**, 286, 802 (1924).

¹⁶³ Darzens, *Compt. rend.*, **150**, 707 (1910).

¹⁶⁴ Wieland and Bettag, *Ber.*, **55**, 2246 (1922).

¹⁶⁵ Cook and Lawrence, *J. Chem. Soc.*, 1637 (1935).

full equivalent of the metal halide. A number of these complexes were isolated by Perrier,¹⁶⁶ and Kohler¹⁶⁷ found from boiling-point and freezing-point determinations that the Perrier compounds invariably are composed of two molecules of the carbonyl compound and one ("double") molecule of aluminum halide: $\text{Al}_2\text{X}_6 \cdot 2\text{RCOCl}$, and $\text{Al}_2\text{X}_6 \cdot 2\text{R}_2\text{CO}$. It was established further that the complexes are not formed by addition to the carbonyl group, for aluminum halides form double compounds with ethers as well as with carbonyl compounds. With this observation, Kohler characterized the Perrier compounds as oxonium salts, and the work was confirmed and extended by Pfeiffer.¹⁶⁸ Kohler employed the



noncommittal formulation IV, for the benzoyl chloride complex, and a possible interpretation is given in formula V.

Oddly enough, instead of playing an essential part in the ketone synthesis, these complexes if anything hinder the reaction. This is particularly true of the double compound of the ketone formed in the condensation. It is because the ketone binds aluminum chloride so firmly as to render it unavailable for catalysis that a molecular equivalent of the halide is required to complete the reaction. The complex from the acid chloride, although it is not measurably dissociated in boiling carbon disulfide solution, appears to be somewhat less stable, for Olivier¹⁶⁹ found that the addition of benzophenone to a solution containing the Perrier compound from benzoyl chloride and aluminum chloride prevented the reaction of this compound with benzene. The ketone evidently abstracts the metal halide from the acid chloride complex. Olivier observed further that a slight excess of free aluminum chloride has a stronger catalytic action than that bound by the acid chloride. The Perrier compounds therefore are not concerned with the actual substitution reaction, and their formation in the course of one type of Friedel and Crafts condensation is fortuitous.

Many years ago Gustavson¹⁷⁰ isolated labile complexes from benzene or toluene and metal halides, for example $\text{AlBr}_3 \cdot 3\text{C}_6\text{H}_6$ (or possibly $\text{Al}_2\text{Br}_6 \cdot 6\text{C}_6\text{H}_6$), and he suggested that these secondary valence compounds may activate the ring for reaction with halogens. The idea was

¹⁶⁶ Perrier, *Compt. rend.*, **116**, 1140, 1298 (1893); **119**, 276 (1894).

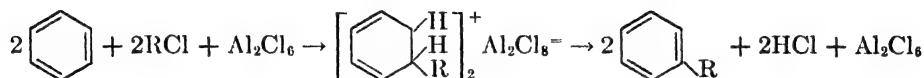
¹⁶⁷ Kohler, *Am. Chem. J.*, **24**, 385 (1900); **27**, 241 (1902).

¹⁶⁸ Pfeiffer and Haack, *Ann.*, **460**, 156 (1928).

¹⁶⁹ Olivier, *Chem. Weekblad*, **11**, 372 (1914).

¹⁷⁰ Gustavson, *Ber.*, **13**, 157 (1880); **16**, 784 (1883).

later elaborated and applied to the Friedel and Crafts reaction by Schaarschmidt,¹⁶² but there is as yet no evidence that such complexes play a part in the actual reaction. Since Gustavson's complexes are stable only at a temperature considerably below that ordinarily maintained in the reactions, it is indeed unlikely that they are concerned with the substitutions. If intermediate complex formation constitutes an essential step in the substitution, this more probably involves a combination between the organic halide, the metal halide, and the hydrocarbon. From anthraquinone, a carbonyl compound incapable of undergoing the Friedel and Crafts reaction, Kohler¹⁶⁷ succeeded in isolating a complex containing three components, $\text{Al}_2\text{Br}_6 \cdot \text{C}_{14}\text{H}_8\text{O}_2 \cdot 2\text{C}_6\text{H}_6$. When a reactive carbonyl component (acid chloride, anhydride) is used, it is possible that a similarly constituted but labile complex is formed. In view of the clear analogy between the Friedel and Crafts reaction and the process of catalytic halogenation, the most plausible formulation is perhaps that of Pfeiffer and Wizinger.

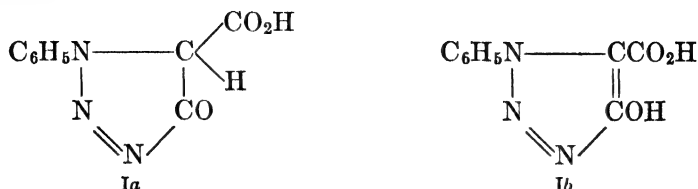


Reactions of Phenols and Amines. Certain substitution reactions are so specific to phenols and amines, in contrast to other aromatic compounds, that it will be well to consider the possibility that they follow a course different from other substitutions. The coupling reaction, and the related processes of nitrosation and condensation with *p*-nitrosodimethylaniline, fall into this category; other specific substitutions include the rapid, non-catalytic halogenation of phenols and amines in dilute solution, the condensation of these substances with aldehydes, and the formation of various types of C-alkyl derivatives. It is significant that all these reactions are characteristic as well of the aliphatic enols, and the mechanism probably is essentially the same with the two types. The possibility¹⁷¹ that the substitution reactions of either the phenols or their aliphatic prototypes is associated in any way with a process of tautomerism may be eliminated. Dimroth¹⁷² examined several pairs of aliphatic keto-enol tautomers which were known not to undergo appreciable change under conditions suitable for coupling experiments (in alcohol at 0°) and found that only the enolic forms react with *p*-nitrobenzenediazoic acid: $\text{—C(OH)=CH—} \rightarrow \text{—C(OH)=C(N=NAr)—}$. The examples included one pair of a near-aromatic type, 1-phenyltriazolone-5-carboxylic acid (Ia) and the corresponding

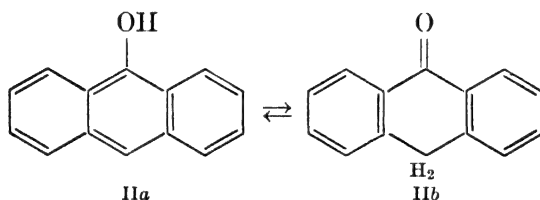
¹⁷¹ Thiele, *Ann.*, **306**, 129 (1899).

¹⁷² Dimroth, *Ber.*, **40**, 2404 (1907).

enol. While the keto form (Ia) failed to react, the enol (Ib) coupled with displacement of the carboxyl group.



A test of the point in the aromatic series became possible with K. H. Meyer's¹⁷³ isolation of the pure tautomers anthranol (IIa) and anthrone (IIb). While phenols and naphthols show little tendency to ketonize, the isomerization of the 9-hydroxy derivative of anthracene is favored both by the reactive *o*-quinonoid structure of the enol and by the stabilizing influence on the central nucleus of the keto form exerted by the two flanking benzene rings. The cold solution in alcohol contains at equilibrium 89 per cent of the nearly colorless, non-fluorescent anthrone, while pyridine produces complete isomerization to anthranol, a yellow substance which is strongly fluorescent in dilute solutions. Acetone, as

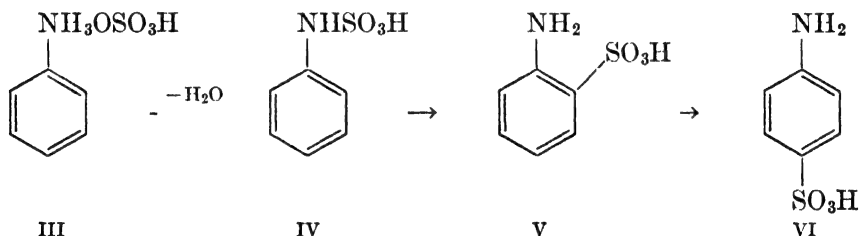


compared with alcohol, displaces the equilibrium in favor of the keto form. In suitable solvents, and in the absence of acids or bases, the change from one form to the other occurs sufficiently slowly to enable tests to be made of the reactivity of each tautomer, and Meyer found that anthranol alone enters into reactions characteristic of phenols. Anthranol couples easily with diazotized amines and is oxidized at once to dianthrone, while anthrone reacts in each case only to the extent that it isomerizes under the conditions of the experiment. There is no justification for attempting to associate the special properties of phenols and amines with the evidently fortuitous fact that these compounds theoretically are capable of reacting in tautomeric forms, for in a test case it is established that the ketonic modification is wholly devoid of reactivity.

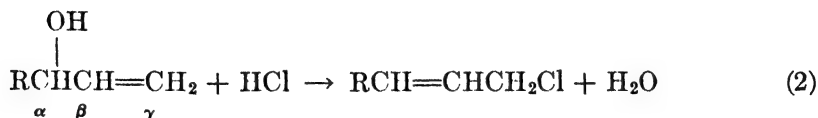
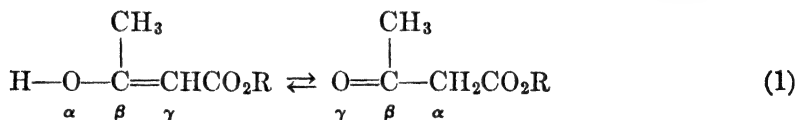
Another possibility is that the mobile hydrogen atoms of the OH and NH₂ groups suffer temporary replacement by the substituting radical. The substituent may first enter the hydroxyl or amino side chain

¹⁷³ Meyer, *Ann.*, **379**, 37 (1911).

and then rearrange to the nucleus, and the hypothesis that the characteristic reactions proceed by an indirect substitution¹⁷⁴ or "side-chain catalysis" is lent plausibility by the fact that certain substitutions definitely follow the course of a true intramolecular rearrangement. A case in point is in the preparation of sulfanilic acid from aniline sulfate. Bamberger¹⁷⁵ showed that the aniline sulfate loses water on being heated and gives phenylsulfamic acid, IV, which can be prepared also by condensing phenylhydroxylamine with sulfur dioxide, the product being isolated as the stable sodium salt. On moderate heating, the sulfonic acid group of IV migrates to the ring to give orthanilic acid, V, which, at a higher temperature (180°), rearranges to the *p*-isomer, VI. The formation of *ortho* and *para* compounds is in marked contrast to the production of metanilic acid by the direct sulfonation of aniline sulfate with fuming sulfuric acid. The rearrangements were interpreted by Lapworth¹⁷⁶ in



terms of his α, γ -rule, which in this connection has no theoretical implications other than the assumption of the Kekulé formula, but which is of great value in correlating a large number of intramolecular shifts. In the enol \rightarrow keto change, or the reverse, hydrogen migrates from the α - to the γ -position, with transposition of the double bond to the original α, β -



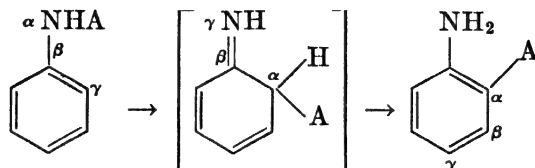
position (1), while in the allylic rearrangement (2) a similar process occurs in the course of the exchange of groups. In the case of an amine

¹⁷⁴ van Alphen, *Rec. trav. chim.*, **46**, 804 (1927). See, also, Blanksma, *ibid.*, **21**, 281 (1902).

¹⁷⁵ Bamberger and Hindermann, *Ber.*, **30**, 654 (1897); Bamberger and Kunz, *Ber.*, **30**, 2274 (1897).

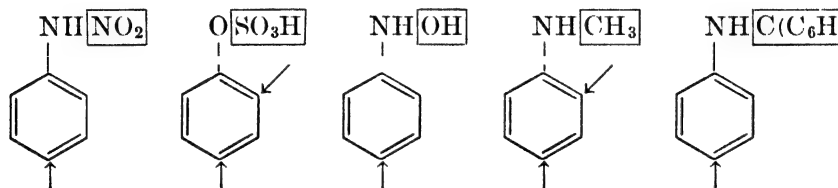
¹⁷⁶ Lapworth, *J. Chem. Soc.*, **73**, 445 (1898).

or phenol derivative, the α, γ -migration of the group A is followed by an α, γ -shift of hydrogen in the reverse direction. The *para* position is

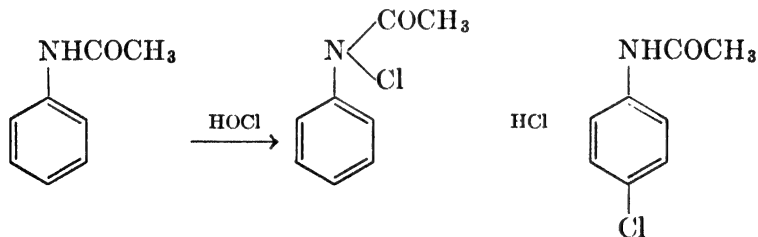


reached by a second migration in the new α, γ -system. This interpretation accounts adequately for the fact that *meta* derivatives are never formed by true rearrangements.

Other examples of rearrangements (p. 965), with indications of the nature and direction of the migrations, are given in the accompanying formulas.



In the first three, rearrangement is brought about at low temperatures by treatment with acids; N-methylaniline rearranges when the hydrochloride is heated to about 300° , while migration of the triphenylmethyl group occurs at 160° in the presence of zinc chloride. The question of whether reactions of this type proceed by a true intramolecular migration or intermolecularly has been investigated particularly with reference to the conversion of N-chloroacetanilide into *p*-chloroacetanilide under the influence of acids. From an extensive study of the problem, Orton

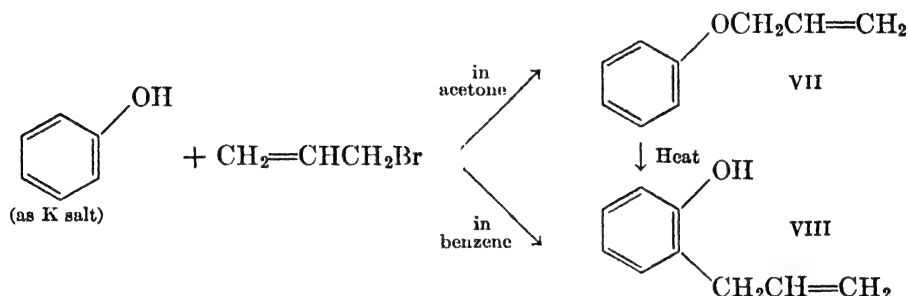


and co-workers * concluded that in aqueous acid solution the chloroamine suffers hydrolysis, $\text{C}_6\text{H}_5\text{N}(\text{Cl})\text{COCH}_3 + \text{HCl} \rightarrow \text{C}_6\text{H}_5\text{NHCOCH}_3 + \text{Cl}_2$, and acts as a source of chlorine for a nuclear substitution. Olson

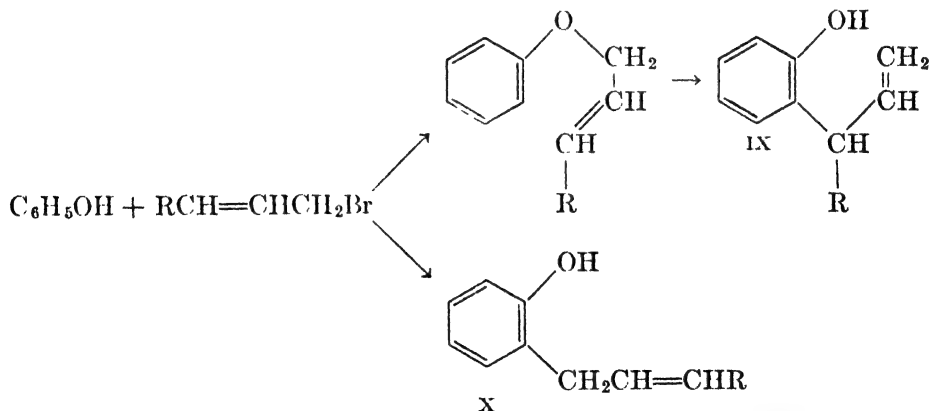
* The principal evidence is summarized in the following papers and reviews: Orton and Jones, *Brit. Assoc. Advancement Sci. Repts.*, 1910, p. 85; Orton, Soper, and Williams *J. Chem. Soc.*, 998 (1928); Ingold, *Ann. Repts. Chem. Soc. (London)*, **24**, 154 (1927).

and co-workers¹⁷⁷ studied the rearrangement in the presence of radioactive hydrochloric acid, however, and concluded that the reaction proceeds partly as suggested by Orton and partly by a more complex process.¹⁷⁸ Bell¹⁷⁹ has reported that in non-dissociating solvents the reaction is probably intramolecular.

A particularly clear distinction between rearrangement and direct substitution can be made in the case of the formation of *o*-allylphenols by the methods discovered by Claisen.¹⁸⁰ Claisen found that potassium phenolate can be converted by the action of allyl bromide largely into either the O-allyl or the C-allyl derivative according as an ionizing or a non-ionizing solvent is employed, and he also observed that the allyl ether VII rearranges to *o*-allylphenol (VIII) on being heated.



From these facts alone it might be supposed that in the course of reaction in benzene solution the ether is formed and rearranges to the nuclear substitution product VIII, but it was found that the ether does not rearrange under the conditions of the alkylation. An absolute proof of



¹⁷⁷ Olson, Porter, Long, and Halford, *J. Am. Chem. Soc.*, **58**, 2467 (1936).

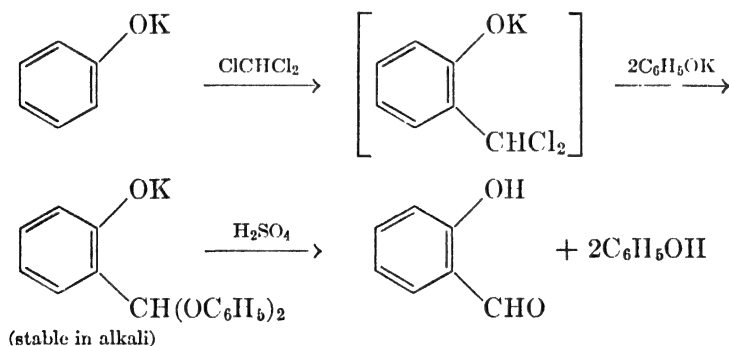
¹⁷⁸ Olson and Hornel, *J. Org. Chem.*, **3**, 76 (1938).

¹⁷⁹ Bell, *J. Chem. Soc.*, 1154 (1936).

¹⁸⁰ Claisen, *Z. angew. Chem.*, **36**, 478 (1923); Claisen, Kremers, Roth, and Tietze, *Ann.*, **442**, 210 (1925); Claisen and Tietze, *Ann.*, **449**, 81 (1926). See Torbell, *Chem. Rev.*, **27**, 495 (1940).

the point is furnished by introducing a marking substituent in the allyl group, for then the product (IX) obtained by O-alkylation and rearrangement is found to have the alkyl group in the α -position of the allyl chain, whereas the direct alkylation in benzene gives a γ -substituted *o*-allylphenol, X. The Claisen rearrangement may proceed through an α,γ -shift, or allylic transformation, with respect to both the nucleus and the hydrocarbon group,¹⁸¹ but it is evident that the process is entirely distinct from that of direct C-alkylation. A knowledge of the course of the former reaction consequently is of no value in elucidating the mechanism of the substitution. The same distinction exists between the rearrangement of allyl ethers of aliphatic enols and the C-allylation of the enols. With respect to direct substitution, the enols differ from the usual phenols only in being sufficiently reactive to yield C-alkyl derivatives with saturated alkyl halides, while phenols react in this way only with the more reactive β,γ -unsaturated alkyl halides. In the case of anthranol, however, the distinction vanishes for, owing to the enhanced reactivity of the central nucleus, C-alkylation occurs in part in the reactions with methyl and ethyl iodide.

A direct C-alkylation probably is involved also in the first step of the Reimer-Tiemann reaction, in the manner indicated in the formulas. The succeeding steps have been established definitely by Armstrong.¹⁸²



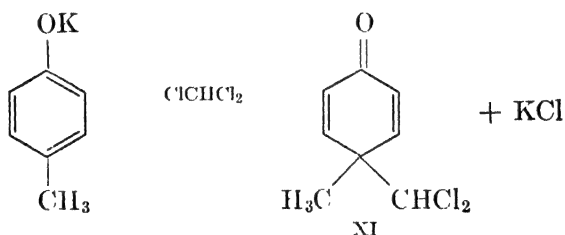
Although the dichloromethyl derivative of phenol has not been isolated, evidence that such an intermediate is produced is afforded by the work of von Auwers,¹⁸³ who discovered an interesting type of by-product in investigating the reaction of chloroform with various alkylated phenols in

¹⁸¹ Lauer and Filbert, *J. Am. Chem. Soc.*, **58**, 1388 (1936); Lauer and Ungnade, *ibid.*, **58**, 1392 (1936), have reported the anomalous rearrangement $\text{C}_6\text{H}_5\text{OCH}_2\text{CH}=\text{CHCH}_2\text{CH}_3 \rightarrow \text{C}_6\text{H}_4(\text{OH})(\text{CH}(\text{CH}_3)\text{CH}=\text{CHCH}_3$.

¹⁸² Armstrong and Richardson, *J. Chem. Soc.*, 496 (1933).

¹⁸³ v. Auwers and Winternitz, *Ber.*, **35**, 465 (1902); v. Auwers and Keil, *Ber.*, **35**, 4207 (1902). Woodward, *J. Am. Chem. Soc.*, **62**, 1208 (1940), has applied the reaction to the synthesis of polynuclear compounds having angular methyl groups.

alkaline medium. *p*-Cresol, for example, was found to yield in addition to a hydroxyaldehyde a considerable quantity of a crystalline compound which was fully characterized as the chloroketone XI. The substance is hydrolyzed only with difficulty, it reacts with the usual ketone reagents, and on reduction it yields *p*-cresol and methylene chloride. Rather than block this form of substitution, alkyl groups seem to promote reaction at the point of their attachment to the nucleus, and the chloroketones are sometimes formed in yields as high as 40 per cent of the theoretical amount. The formation of these compounds shows clearly that the entrance of the dichloromethyl group into the ring, as supposed above, is possible. The observation also provides a significant clue regarding the mechanism of C-alkylation, and consequently of the other specific substitution reactions of phenols and amines. The chloroketone XI cannot



arise by a process of direct replacement, and a condensation of chloroform with the keto form of *p*-cresol is excluded by the evidence presented above and by the fact that the reaction is conducted in a strongly alkaline medium. The reaction must involve some form of addition of chloroform to the unsaturated nucleus, followed by the loss of potassium chloride. The reaction is particularly significant because it involves the transformation of an aromatic ring into a dihydrobenzenoid ring.* Such a change is observed frequently with the polynuclear compounds but, because of the adverse energy relationships, is rarely encountered in the benzene series. The occurrence of the addition is particularly remarkable because an alternate path is open leading to the formation of the *o*-hydroxyaldehyde. For these reasons this case of addition can hardly be dismissed as an abnormal side reaction but must be regarded as intimately associated with the process leading to the more usual C-alkylation.

The coupling reaction of amines and phenols and the process of nitrosation are appropriately considered together. The similarity be-

* It is important to note that the chloroketone XI does not have a quinonoid structure, for only one of two *para* carbon atoms is doubly bound to another element. The degree of unsaturation and conjugation is considerably less than that of a quinone or a quinonoid compound and the substance is colorless. The corresponding quinol (OH in place of CHCl_2) is likewise colorless.

tween these two processes extends to the conditions and limits of the reactions, the orientations, and the structures of the reagents, at least in the forms $\text{HO}-\text{N}=\text{O}$ and $\text{HO}-\text{N}=\text{NC}_6\text{H}_5$. The latter formula is that of the substance resulting from the hydrolysis of benzenediazonium chloride, $[\text{C}_6\text{H}_5\text{N}\equiv\text{N}]^+ + \text{OH}^- \rightleftharpoons \text{C}_6\text{H}_5\text{N}=\text{NOH}$ (the hydrolysis constant at 0° is 1.25×10^{-3}).^{*} In the early literature the substance was termed benzenediazohydrate or benzenediazohydroxide, but, since it is a weak acid comparable with nitrous acid and forms metal salts which are called diazotates, the name benzenediazoic acid seems preferable. Conant and Peterson¹⁸⁴ studied the kinetics of the coupling of diazotized amines with phenols in the region pH 5-8 and found that the rate of the bimolecular coupling reaction increases regularly with increasing hydroxyl-ion concentration. The amount of aryldiazoic acid present in equilibrium with the diazonium ion increases with increasing pH, and Conant and Peterson interpreted their data as indicating that coupling occurs between the aryldiazoic acid and the undissociated phenol. Goldschmidt¹⁸⁵ had observed in qualitative experiments that alkali in excess has a retarding influence on the reaction, and this could be due partly to the removal of the phenol from the equilibrium as the phenoxide ion and partly to a decreased concentration of the aryldiazoic acid by virtue of its acidic ionization. Wistar and Bartlett,¹⁸⁶ however, have pointed out that the results agree equally well with the hypothesis that coupling occurs between the diazonium ion and the phenoxide ion. These investigators studied the rate of coupling of diazonium salts with amines in the pH range 2-6 and found that the velocity at first increases with increasing pH and then reaches a plateau value. Their kinetic data are consistent with only one plausible interpretation, namely, that the coupling is between the diazonium ion and the free amine. Although the quantitative studies have not been extended to the alkaline range, it seems probable that in all cases the diazonium ion constitutes one of the active coupling components and that the second component is the free amine or the phenoxide ion. In the following discussion of the general problem the aryldiazoic formulation is used both as a matter of convenience in outlining earlier views and in order not to lose sight of the marked analogy between the processes of coupling and of nitrosation.

The possibility that the coupling of a phenol proceeds by attachment of the diazo group to oxygen and subsequent rearrangement of the diazo

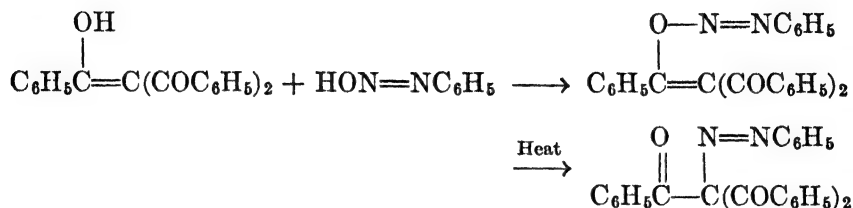
^{*} For a review of the properties and structures of the diazo compounds, see Saunders, "The Aromatic Diazo Compounds," Longmans, Green and Co., London (1936), pp. 173-213.

¹⁸⁴ Conant and Peterson, *J. Am. Chem. Soc.*, **52**, 1220 (1930).

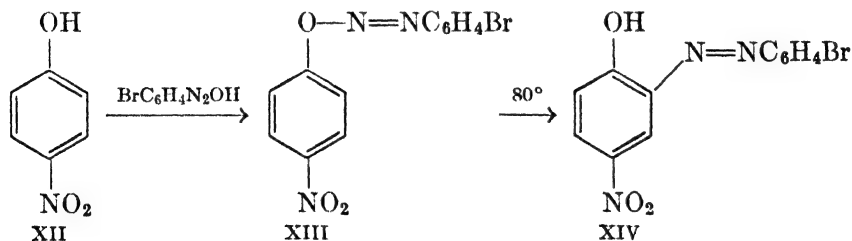
¹⁸⁵ Goldschmidt and Merz, *Ber.*, **30**, 670 (1897); *Ber.*, **35**, 3534 (1902).

¹⁸⁶ Wistar and Bartlett, *J. Am. Chem. Soc.*, **63**, 413 (1941).

ether was discussed as early as 1870 by Kekulé,¹⁸⁷ and the hypothesis was given prominence by Dimroth's¹⁸⁸ discovery of ethers of this type. From the enolic form of tribenzoylmethane (potassium salt), Dimroth obtained a yellow diazo ether which isomerizes when heated above the melting point to a red C-azo compound. From the interaction of *p*-



bromobenzenediazoic acid and *p*-nitrophenol in the presence of soda and alcohol, he succeeded in preparing the labile diazo ether XIII. The substance is easily cleaved by acids to *p*-nitrophenol and a *p*-bromobenzenediazonium salt, it gives up the diazo group to β -naphthol with liberation of *p*-nitrophenol, and it is converted into a true *o*-azophenol, XIV, on being heated gently. That the ether is sufficiently stable to be isolated is probably due to the influence of the nitro group in rendering the aromatic ring less susceptible to the entrance of the diazo group, but Dimroth recognized that the use of the rather strongly acidic *p*-nitrophenol has the theoretical disadvantage that the product may be merely a diazonium salt $[\text{BrC}_6\text{H}_4\text{N}\equiv\text{N}]^+\text{O}_2\text{NC}_6\text{H}_4\text{O}^-$. In a later investigation,¹⁸⁹ however, it was found that the substance has very little conductivity and consequently is not a salt. A true diazo ether was prepared



also from the weakly acidic pentamethylphenol, in which nuclear substitution is impossible, the other component being the unusually stable diazonium salt from 4-benzoylamino-1-naphthylamine. The properties of the substance are essentially as outlined above, and the conductivity is negligible. The product obtained from picric acid, on the other hand,

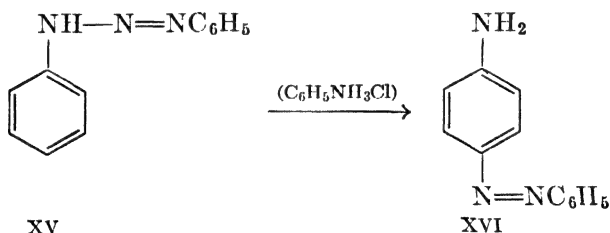
¹⁸⁷ Kekulé and Hidegh, *Ber.*, **3**, 233 (1870).

¹⁸⁸ Dimroth and Hartmann, *Ber.*, **41**, 4012 (1908).

¹⁸⁹ Dimroth, Leichtlin, and Friedemann, *Ber.*, **50**, 1534 (1917).

proved to be a diazonium salt and not a diazo ether. Diazo ethers have been prepared also from 1-halo-2-naphthols.¹⁹⁰

While the isolation of diazo ethers seemed to Dimroth to support the hypothesis that the ordinary coupling reaction proceeds through the formation and rearrangement of an intermediate ether, no evidence has been presented to show whether these substances are essential to the coupling process, or merely incidental products formed in an independent reaction. By analogy with the similarly constituted N-azo compounds, it may be inferred with reasonable assurance that they are not concerned in the actual process of substitution. Diazoaminobenzene (XV) results from the interaction of benzenediazonium chloride and aniline in a neutral or alkaline medium, and it is reconverted by hydrochloric acid into the components, or their transformation products. Conversion of the N-azo compound into *p*-aminoazobenzene (XVI) can be brought about in a solution of the substance in aniline containing aniline hydrochloride or in an alcoholic solution of hydrochloric acid, zinc chloride, or calcium chloride. The reaction is unimolecular¹⁹¹ and subject to acid catalysis, but the acidity must be kept below the point of total cleavage. The chief reason for believing that the reaction does not follow the course of an intramolecular rearrangement is that the diazo group can be captured by a foreign amine which has a sufficiently greater susceptibility to nuclear substitution.¹⁹² When submitted to



“rearrangement” in the presence of dimethylaniline, diazoaminobenzene yields a considerable amount of *p*-dimethylaminoazobenzene. The $\text{C}_6\text{H}_5\text{N}=\text{N}-$ residue also can be transferred from diazoaminobenzene to the more reactive nucleus of *m*-toluidine.¹⁹³ Of further significance is the observation of K. H. Meyer¹⁹³ that the direct coupling of primary amines of the benzene series, without the preliminary formation of a diazoamino compound, can be realized by using a particularly reactive diazo component, by employing an amine of enhanced reactivity, or by conducting the reaction in a medium of such acidity that the N-azo

¹⁹⁰ Rowe and Peters, *J. Chem. Soc.*, 1065 (1931).

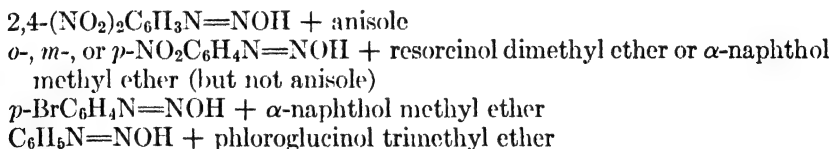
¹⁹¹ Goldschmidt and Reinders, *Ber.*, **29**, 1369, 1899 (1896); Goldschmidt and Salcher *Z. physik. Chem.*, **29**, 89 (1899).

¹⁹² Rosenhauer and Unger, *Ber.*, **61**, 392 (1928).

¹⁹³ Meyer, *Ber.*, **54**, 2265 (1921).

compound is not stable. Examples of these processes are found in the formation of aminoazo compounds, rather than diazoamino derivatives, in the following cases: *p*-nitrobenzenediazoic acid + aniline, benzenediazoic acid + *m*-toluidine or *m*-phenylenediamine, benzenediazoic acid + aniline (in aqueous formic acid solution). As stated in an earlier section, direct coupling even in a neutral medium is the rule with the primary amines of the naphthalene series, owing to their reactivity. These observations all indicate that N-azo and C-azo compounds are formed in independent reactions. The apparent "rearrangement" of diazoaminobenzene probably involves acid cleavage to the diazonium salt and the amine, followed by a more rapid recombination of the components to give the nuclear substitution product. Since the acid concentration would remain constant in a given experiment, the rate-controlling reaction would be unimolecular. It is concluded that N-azo compounds, and by inference O-azo compounds, are not essential to the actual process of substitution in the coupling reaction.

In addition to the evidence that an indirect substitution is not involved in the coupling of phenols and primary amines, it is significant that tertiary amines, with which intermediate substitution in the side chain is not possible, couple readily with diazo components. K. H. Meyer¹⁹⁴ discovered that many phenol ethers also are capable of coupling, although combination takes place less readily than with the corresponding free phenols. Some augmentation of the driving force is required, and Meyer found that this can be accomplished by suitable activation of either component. The introduction of nuclear nitro groups or halogen atoms increases the coupling power of the diazo component, while alkyl or alkoxy groups in the *meta* position enhance the reactivity of a given ether. Conducting the coupling in glacial acetic acid solution in the presence of sodium acetate, Meyer obtained azo compounds in the following typical cases:

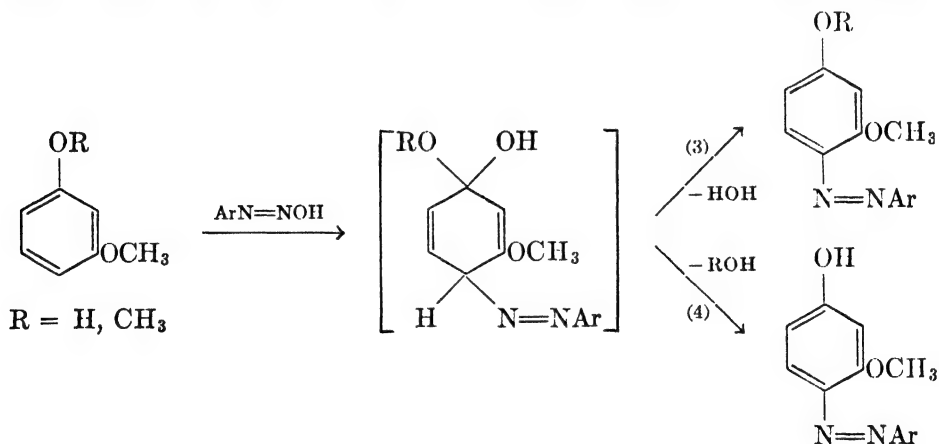


The acetyl derivatives of phenols and amines do not react under comparable conditions. Nitrous acid was found to react with α -naphthol methyl ether with loss of the methyl group.

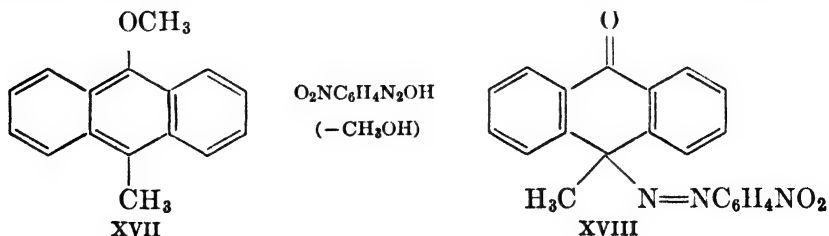
The fact that many phenol ethers and dialkylamines enter into the coupling reaction even though they are incapable of forming inter-

¹⁹⁴ Meyer and Lenhardt, *Ann.*, **398**, 74 (1913); Meyer, Irschick, and Schlösser, *Ber.*, **47**, 1741 (1914).

mediate O-azo or N-azo compounds is a strong indication that such intermediates are not essential to the coupling of free phenols and of primary and secondary amines. There is little justification for supposing that phenol ethers couple by a path different from that taken by the phenols simply because they react somewhat less readily, since a high degree of reactivity is displayed by the dialkyl derivatives of aniline. As an alternate mechanism, applicable to the alkyl derivatives and free hydrogen compounds alike, Meyer suggested that coupling proceeds by an addition-elimination process. The *para* coupling of a free phenol is regarded as a 1,4-addition to the conjugated system of the nucleus, followed by the loss of water, either across the ring (3) or from the methylenedihydroxy group (4), and enolization. In the case of an ether, the second mode of elimination may take precedence and lead to hydrolysis, and indeed such a result frequently is observed. According to this view the function of the hydroxyl or amino group is simply to activate the unsaturated system for addition. In support of the suggested mechanism is the observation of Meyer that the methyl ether of 10-methyl-9-anthranol, XVII, reacts with *p*-nitrobenzenediazoic acid to give a substance characterized as the methylarylazoanthrone XVIII.

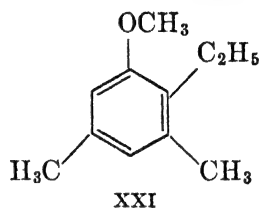
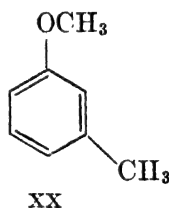
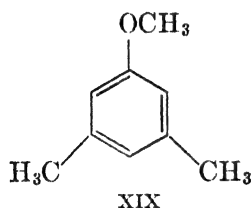


in this case, and according to the above scheme this takes the usual course (4) except that enolization cannot occur in the final step.

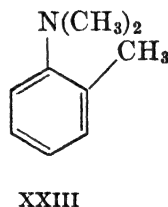
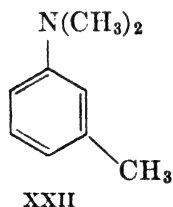


The observations of Meyer concerning the coupling of ethers were extended by von Auwers,¹⁹⁵ who compared the action of *p*-nitrobenzene-diazoic acid on a large number of alkylated phenols and their ethers. The most significant outcome of this work was the recognition of a very interesting difference in the influence of substituent groups depending on their location in the nucleus. In agreement with the observations of Meyer, von Auwers found that alkyl (or alkoxy) groups in the *meta* position to the functional group of a phenol or ether facilitate coupling, but he observed that alkyl groups in the *ortho* position had no activating, and perhaps a slight inhibiting, effect. *m*-Xylenol ether (XIX), for example, couples more readily than *m*-cresol ether (XX) or perhaps than *o*-ethyl-*m*-xylenol ether (XXI). Coupling occurs with the methyl ether of *m*-cresol, but not with that of *o*-cresol.

The influence of a *meta* alkyl group is understandable, for this type of group would be expected to facilitate substitution at an adjacent



position. It seems remarkable, however, that the substitution should be hindered by a group in the remote *ortho* position. The blocking effect of an *ortho* group has not been definitely established in the phenol ether series but has been observed strikingly in the reactions of amines. While dimethyl-*m*-toluidine (XXII) couples easily with diazotized amines, gives a nitroso derivative, and condenses with aldehydes, these reactions fail entirely or proceed only slowly or under special conditions



in the case of dimethyl-*o*-toluidine, XXIII.¹⁹⁶ * This amine does not react with nitrous acid, with formaldehyde (except under forcing condi-

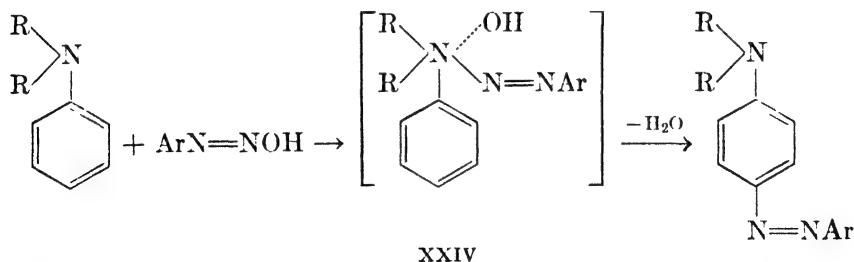
¹⁹⁵ v. Auwers and Michaelis, *Ber.*, **47**, 1275 (1914); v. Auwers and Borsche, *Ber.*, **48**, 1716 (1915).

¹⁹⁶ Friedlaender, *Monatsh.*, **19**, 627 (1898).

* For further examples, see Gnehm and Blumer, *Ann.*, **304**, 87 (1899).

tions), or with benzenediazoic acid, although a coupling can be achieved with the more active *p*-nitrobenzenediazoic acid.¹⁹⁷ The same striking hindrance to the reactions has been observed¹⁹⁶ with the *o*-methoxy, *o*-chloro, and *o*-nitro derivatives of dimethylaniline, all of which behave exactly like the *o*-methyl compound. Friedlaender¹⁹⁶ noted an abnormality in the physical properties of all these unreactive compounds. While in the *meta* and *para* series there is a steady increase in boiling point on passing from the toluidine to the mono- and dimethyl derivatives, in the *ortho* series the dimethyl compound boils at a lower temperature (183°) even than the toluidine (198°). The monomethyl compound (207°) occupies a normal position and is normally reactive. The fact that *ortho* groups of different types exert a similar influence suggests that the effect is of a steric, rather than a chemical, nature (see p. 212).

Karrer¹⁹⁸ reported experiments indicating that in the series of dialkylanilines large N-alkyl groups inhibit *para* nitrosation, and that one of the alkyl groups may be eliminated in the course of diazo coupling. In subsequent work, however, Hickinbottom and co-workers¹⁹⁹ succeeded in obtaining *p*-nitroso derivatives of dibutyl- and diamylanilines and in effecting normal couplings of diazotized sulfanilic acid with the amines studied by Karrer, and with others having still larger alkyl groups. It nevertheless appears that *para* substitutions are repressed to some extent by large N-alkyl groups as well as by other substituents. Goldschmidt¹⁸⁵ found that the velocity constant for the coupling of diethylaniline is only one-sixth that for dimethylaniline. As a possible explanation of both types of hindrance, Karrer suggested that coupling may involve the formation and rapid rearrangement of the intermediate ammonium salt XXIV.



Some analogy is afforded by the work of von Braun,²⁰⁰ who observed a

¹⁹⁷ Bamberger, *Ber.*, **28**, 843 (1895); Bamberger and Meimberg, *Ber.*, **28**, 1891 (1895).

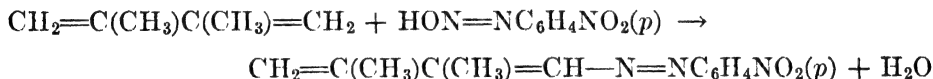
¹⁹⁸ Karrer, *Ber.*, **48**, 1398 (1915).

¹⁹⁹ Reilly and Hickinbottom, *J. Chem. Soc.*, **113**, 99 (1918); Hickinbottom and Lambert, *ibid.*, 1383 (1939).

²⁰⁰ v. Braun, *Ber.*, **49**, 1101 (1916); v. Braun, Arkuszewski, and Köhler, *Ber.*, **51**, 282 (1918).

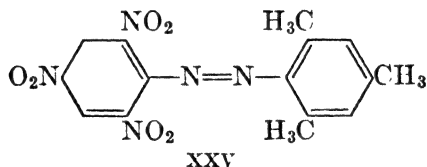
parallelism in the ease of alkylation of *o*-substituted dimethylanilines and in the ease of *p*-substitutions of the compounds. Whatever plausibility this mechanistic picture may have as applied to amine coupling, it seems hardly admissible as an interpretation of the coupling of a phenol or phenol ether, for an oxonium salt can have little reality in an alkaline medium.

Another possibility is that coupling proceeds by some form of addition to the unsaturated system of the aromatic nucleus. The formation of ketonic products in the Reimer-Tiemann reaction, in the coupling of an alkylanthranol, and in the bromination and nitration of 1-substituted β -naphthols points in this direction. Of further significance is K. H. Meyer's²⁰¹ discovery that in certain cases coupling can be accomplished with compounds having no hydroxyl or amino groups. In the aliphatic series, azo compounds were obtained from butadiene, isoprene, piperylene, and, particularly readily, from 2,3-dimethylbutadiene.



With an active diazo component having one or two nitro groups, coupling occurs readily in glacial acetic acid solution or in alcohol. Since the formation of the azo compound is recognizable from the appearance of a characteristic color, the reaction has been found useful as a test method for establishing the presence of a conjugated system of linkages in open-chain²⁰² and alicyclic compounds.²⁰³

Meyer and Tochtermann²⁰¹ found that the extremely reactive diazonium salt from picramide couples rapidly with mesitylene to give in good yield the azo compound XXV. L. I. Smith and Paden²⁰⁴ later observed



that pentamethylbenzene (XXVI) and isodurene (XXVII) yield trinitrobenzeneazo compounds, but that the reaction fails in the case of

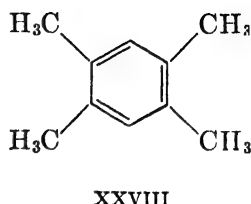
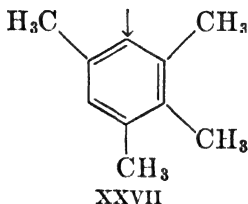
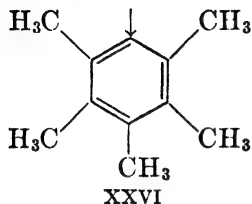
²⁰¹ Meyer, *Ber.*, **52**, 1468 (1919); Meyer and Tochtermann, *Ber.*, **54**, 2283 (1921).

²⁰² Terentiev and co-workers, *Compt. rend. acad. sci. U.R.S.S.*, **4**, 267 (1935); *Sci. Repts. Moscow State Univ.*, **6**, 257 (1936); *J. Gen. Chem. (U.S.S.R.)*, **7**, 2026 (1937); **8**, 662 (1938); Arbusov and Rafikov, *ibid.*, **7**, 2195 (1937).

²⁰³ Fieser and Campbell, *J. Am. Chem. Soc.*, **60**, 159 (1938).

²⁰⁴ Smith and Paden, *ibid.*, **56**, 2169 (1934).

durene (XXVIII). In each of the three compounds which couple, a position in the ring is activated by the directive influence of two *ortho* groups and one *para* group, while durene lacks the feature of *para* direction. Still more striking is the observation referred to in an earlier section



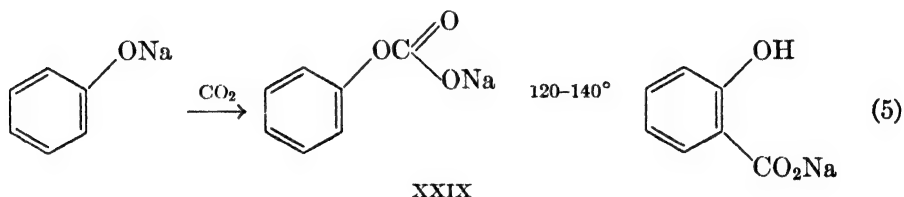
(p. 174) that 3,4-benzpyrene couples readily with the only moderately active diazonium salt from *p*-nitroaniline.

These observations are important in showing that oxygen or nitrogen atoms are not indispensable to the process of coupling, and hence that an intermediate attachment of the diazo component to a hydroxyl or amino group can hardly represent an essential phase of the ordinary coupling reactions. The fact that certain hydrocarbons are capable of forming azo compounds was considered by Meyer to support the addition-elimination mechanism, and in his view hydroxyl or amino groups when present merely activate the ring for addition. The addition mechanism becomes still more attractive if it is extended to include some participation of the key atom of the amines and phenols, as suggested by the blocking effect of groups in the *ortho* position or attached to nitrogen. Such a participation is not unreasonable, because the nitrogen or oxygen atom concerned is unsaturated, having respectively one and two pairs of unshared electrons, and consequently it is in a sense conjugated with the unsaturated system of the nucleus. von Auwers¹⁹⁵ called attention to this feature of the structures and suggested that the systems $C=C-O\cdots$ and $C=C-C=C-O\cdots$, in which the dotted lines represent latent valences, are comparable with $C=C-C=C$ and $C=C-C=C-C=C$. Indeed, similar exaltations of the specific refraction and dispersion have been found for the two types of systems.²⁰⁵ The great reactivity of the phenols, enols, and amines may be due to this type of conjugation, and the entire conjugated system extending to the unsaturated oxygen or nitrogen atom may well be involved in some way in the coupling reaction. It is improbable, however, that the reaction proceeds by an addition in the ordinary sense to give an intermediate of a true dihydrobenzenoid type, as in the formal representation postulated by Meyer. A substantial argument against such an addition is the observation that 3,4-benzpyrene enters readily into the coupling reaction but appears inaccessible

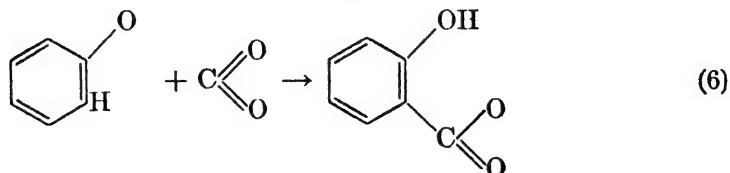
²⁰⁵ v. Auwers, *Ber.*, **44**, 3514 (1911).

to additions. Although the formation of azo compounds from amines and phenols presents certain interesting peculiarities, the reaction does not appear to differ in kind from other aromatic substitutions.

The nitrosation, bromination, aldehyde condensation, and C-alkylation of amines and phenols probably fall into the same category as the coupling reaction. Some further substitutions are known to be the result of intramolecular rearrangement, and there may be still other routes leading to the introduction of substituents. An addition of the aromatic nucleus to an unsaturated linkage of the reagent conceivably may occur in certain cases, for example in the Kolbe synthesis of hydroxy acids. The observation²⁰⁶ that the salicylic acid synthesis can be



accomplished by heating sodium phenyl carbonate (XXIX) suggests that the reaction between sodium phenolate and carbon dioxide may involve the formation and rearrangement of this salt (5). It has been reported,²⁰⁷ however, that sodium phenyl carbonate dissociates into its components at a temperature below that at which the reaction takes place, and, furthermore, known rearrangements of the type pictured do not occur under comparable conditions but require acid catalysis. An alternative proposal²⁰⁷ is that the phenolate nucleus adds to a double bond of carbon dioxide, with readjustment of the charge to the more acidic group (6). Such a mechanism might account for the unusual orientations sometimes observed in the Kolbe reaction. β -Naphthol, heated in the form of the sodium salt with carbon dioxide under pressure, yields the unstable 1-carboxylic acid at 120–145°, but gives the more stable 3-carboxylic acid in the temperature range 200–250°. Substitution at the 3-position seems odd in view of the fact that this position is not available for ordinary reactions requiring an enolic group, even when the 1-position is blocked. A possible explanation is that the 3-acid,



²⁰⁶ Schmitt, *J. prakt. Chem.*, [2] **31**, 397 (1885)

²⁰⁷ Tijmstra Bz., *Ber.*, **38**, 1375 (1905).

which alone is capable of accumulating under the conditions of the experiment, is produced from a small amount of a tautomeric $\Delta^{2,3}$ form of β -naphthol present in equilibrium with the normal $\Delta^{1,2}$ form.²⁰⁸ This implies, however, that the substitution occurs by a rearrangement, and the failure of 1-substituted β -naphthyl allyl ethers to rearrange at the boiling point renders the explanation unlikely. The addition mechanism (6) provides a somewhat more plausible account of the reaction, for the C_3 -hydrogen atom adjacent to the 2-hydroxyl group probably acquires some activation, even though this must be transmitted through a conjugated system of three double bonds, rather than through a double bond at the 2,3-position.

The same mode of addition has been discussed^{144, 195} as a possible mechanism of the coupling reaction, and a more inviting application would be to the condensation of phenols and amines with carbonyl compounds such as Michler's ketone or formaldehyde. It might be supposed that the aromatic component adds, through its mobile *ortho* or *para* hydrogen atom, to the carbonyl group:



Here the addition product would represent the final stage in the reaction, whereas a similar addition to benzenediazoic acid would require the subsequent loss of water. However attractive the hypothesis may appear because of its simplicity, it does not explain the observation that the *p*-condensation with aldehydes, as well as the *p*-coupling, is subject to hindrance by an *ortho* substituent. The reactions with aldehydes and ketones, which proceed best under catalysis by acids or non-metallic halides, probably follow rather the course of other substitutions.

The Directive Influence of Substituent Groups. The problem of accounting for the influence of groups present in the benzene ring on the course of further substitutions has called forth such an enormous amount of experimentation and speculation that a brief review of the subject must be limited to a presentation of the main facts of the case and to a consideration of the more promising interpretations which have been suggested. The principal substituent groups concerned in controlling aromatic substitutions are listed in Table II, and the percentages of *meta* substitution, determined chiefly in carefully studied nitrations, provide an index of the main reaction type. Characteristically *meta* directing and *ortho-para* directing groups are listed in the first two columns, and the third column includes an assortment of substituents derived from the

²⁰⁸ E. Bergmann and Berlin, *J. Org. Chem.*, **3**, 246 (1938).

methyl group. References to the literature may be found in the compilations of Holleman,²⁰⁹ of Ingold,²¹⁰ and of Reese.²¹¹

TABLE II
DIRECTING EFFECTS OF SUBSTITUENT GROUPS *

| <i>Meta</i> Type | | <i>Ortho-Para</i> Type | | Miscellaneous | |
|---|------------------|--------------------------------------|------------------|---|------------------|
| Group | % <i>Meta</i> | Group | % <i>Meta</i> | Group | % <i>Meta</i> |
| --NO ₂ | 93 | --NH ₂ | — | --CH ₂ Cl | 4 |
| --CN | 80 | --NHCOCH ₃ | 2 | --CHCl ₂ | 34 |
| --SO ₃ H | 72 | --N(COCH ₃) ₂ | 1 | --CCl ₃ | 64 |
| --CHO | 79 | --OH | 3 | --C(CO ₂ Et) ₂ | 57 |
| --COCH ₃ | 55 | --OCH ₃ | — | --CH ₂ F | 17 |
| --CO ₂ H | 82 | --CH ₃ | 4 | --CH ₂ Br | 7 |
| --CO ₂ CH ₃ | 73 | --Cl, Br, I | — | --CH ₂ NO ₂ | 50 |
| --CO ₂ C ₈ H ₁₇ (<i>n</i>) | 60 | --C ₆ H ₅ | — | --CH ₂ CH ₂ NO ₂ | 13 |
| --COCl | 90 | --CH ₂ CO ₂ H | — | --CH ₂ NH ₃ ⁺ | 49 |
| --CONH ₂ | 69 | --CH ₂ CN | — | --CH ₂ N(CH ₃) ₃ ⁺ | 88 |
| --NH ₃ ⁺ | 47 | --CH=CHCO ₂ H(R) | — | --(CH ₂) ₂ N(CH ₃) ₃ ⁺ | 19 |
| --N(CH ₃) ₃ ⁺ | 100 | --C≡CCO ₂ H(R) | 8 | --(CH ₂) ₃ N(CH ₃) ₃ ⁺ | 5 |
| --As(CH ₃) ₃ ⁺ | 98 | --CH=CHNO ₂ | — | --CH ₂ P(CH ₃) ₃ ⁺ | 10 |
| --Sb(CH ₃) ₃ ⁺ | 86 | --N=NC ₆ H ₅ | — | --CH ₂ As(CH ₃) ₃ ⁺ | 3 |

* Chiefly in nitrations — indicates that no *meta* substitution is known to occur. Where an ionic group is indicated, the substance nitrated was the sulfate, nitrate, or picrate.

Groups of the predominantly *meta* directing type for the most part contain either a strongly unsaturated group or a positively charged atom adjacent to the ring, while the *ortho-para* directing groups are saturated, or only weakly unsaturated. The introduction of an ethylenic linkage is not sufficient to alter the orienting character of an alkyl group, and the unsaturation of a phenyl group is not strong enough to promote *meta* direction. The *ortho-para* directing methyl group is gradually transformed into a group of the opposite type by the progressive introduction of halogen atoms; the introduction of a single carboxyl group produces no great change, but with three carboxyls the resulting group becomes predominantly *meta* directing. Since the nitro group is more powerful in its influence, the group --CH₂NO₂ directs largely to the *meta* position. Although a number of groups give rise to almost exclusive *ortho-para*

²⁰⁹ Holleman, "Die direkte Einführung von Substituenten in den Benzolkern," Veit & Comp., Leipzig (1910); *Chem. Rev.*, **1**, 189 (1924).

²¹⁰ Ingold, *Ann. Repts. Chem. Soc. (London)*, **23**, 129-143 (1926); see also later volumes.

²¹¹ Reese, *Chem. Rev.*, **14**, 55 (1934).

substitution, marked differences in the relative effectiveness is noted on pitting one group against another in the same molecule, most conveniently in the *para* position. In a competition between the powerful amino group and the weakly orienting methyl radical, for example, the former group controls the substitution. Similar experiments ²¹² have established the following order of decreasing orienting power: $\text{NH}_2 > \text{OH} > \text{OCH}_3 > \text{NHAc} > \text{OAc}$. Relative directive potencies of alkoxyl groups, determined in nitrations of hydroquinone derivatives, are reported ²¹³ as follows: $\text{CH}_3\text{O}(1)$, $\text{C}_2\text{H}_5\text{O}(1.64)$, $n\text{-C}_3\text{H}_7\text{O}(1.80)$, *iso*- $\text{C}_3\text{H}_7\text{O}(2.29)$, $n\text{-C}_4\text{H}_9\text{O}(1.86)$, *tert.*- $\text{C}_4\text{H}_9\text{O}(3.28)$, $n\text{-C}_{16}\text{H}_{33}\text{O}(2.12)$. Among the rather weakly directing halogen atoms, the order is $\text{I} > \text{Br} > \text{Cl} > \text{F}$.

It is of considerable significance that *ortho-para* directing groups, with one exception, facilitate substitution in the ring, while groups of the *meta* type have a retarding influence. Groups of the two types may be said to activate the nucleus for substitution, and to deactivate it, respectively. Toluene, for example, is nitrated fourteen times as fast as benzene; ²¹⁴ the monoalkylation of benzene in the Friedel and Crafts reaction cannot be accomplished without considerable polysubstitution. The progressive introduction of nitro groups, on the other hand, is accomplished with such increasing difficulty that the reaction is easily stopped at any desired stage. The course of the reactions of monosubstituted derivatives of bicyclic compounds such as biphenyl or naphthalene provides a further illustration of the point, for substitution is homonuclear if the group already present is of the *ortho-para* type, and heteronuclear if it is *meta* directing. The one exception to the rule cited is that halogen atoms direct to the *ortho* and *para* positions and yet definitely deactivate the ring and retard substitution.²¹⁴ Since the course of a given substitution is dependent upon the relative velocities of the competing reactions, it is often subject to steric effects. The ratio of *ortho* and *para* isomerides is particularly susceptible to the influence of the steric factor, as can be seen, for example, from the fact that, while the ratio of *ortho* to *para* substitution in the nitration of toluene is 58 : 38, *tert.*-butylbenzene is converted almost exclusively into the *p*-isomer.

Many attempts have been made to formulate a simple rule defining the orientation of the various groups in the hope that this might suggest a clue to the nature of their action. Discussions of the earlier proposals may be found in the reviews by Holleman ²⁰⁹ and by Stewart.²¹⁵ More recently, rules of substitution have been advanced based upon the fol-

²¹² Fuchs, *Monatsh.*, **38**, 331 (1917).

²¹³ Goldsworthy, *J. Chem. Soc.*, 1148 (1936).

²¹⁴ Wibaut, *Rec. trav. chim.*, **34**, 241 (1915).

²¹⁵ Stewart, "Recent Advances in Organic Chemistry," 5th ed., Longmans, Green and Co., London (1927), Vol. I, pp. 322-328.

lowing data: the periodic table,²¹⁶ polarities estimated from electronic configurations,²¹⁷ electric moments,²¹⁸ dissociation constants,²¹⁹ qualitative analogy with inorganic metathetical reactions.²²⁰ A correlation with the effect of nuclear substituents on the rates and equilibria of reactions involving a group in the side chain is indicated in the interesting calculations of Hammett,²²¹ and it has been shown²²² that groups which lower the potential of a parent quinone facilitate substitution in the benzene ring, whereas those which produce an increase in the potential retard benzene substitution (halogen atoms and *meta* directing groups).

The Electronic Theory of Aromatic Substitution (by P. D. Bartlett). Throughout the present century attempts have been made to base an interpretation of aromatic substitution upon the undoubted electrical character of chemical bonds. Early attempts in this direction by Fry²²³ and by Stieglitz²²⁴ assumed a completely polar character for all the carbon-carbon bonds in the benzene ring. A key atom, such as the nitrogen of nitrobenzene, was supposed to induce alternating polarities in the atoms of the rings, and these polarities would determine the orientation with which an attacking reagent could add to one of the double bonds of the ring. The substitution process was regarded as an addition followed immediately by an elimination. The polarity of the key atom could be predicted from its general chemical character. For example, the nitrogen of the nitro group was presumed to be positive with respect to the two oxygens; this made C-1 of the ring negative, C-2 positive, C-3 negative, and so on.

This theory had the merit of self-consistency: the key atoms of the nitro, nitroso, carbonyl, sulfonate, nitrile, and even quaternary ammonium, groups were all seen to be positive and to lead to *meta* direction. The key atoms of the hydroxyl, alkoxyl, and amino groups and the halogen atoms were negative by the same process of reasoning. The theory failed, however, in several important respects. It predicted unequivocally that groups like $-\text{CH}_2\text{NO}_2$ and $-\text{CH}_2\text{N}(\text{CH}_3)_3^+$ should be strongly *ortho-para* directing. The failure of this prediction shows that alternating polarities are non-existent in the side chain and so are not inherent in chemical bonds generally. The theory therefore postulated properties for the bonds in the benzene ring which were apparently with-

²¹⁶ Hammick and Illingworth, *J. Chem. Soc.*, 2358 (1930).

²¹⁷ Latimer and Porter, *J. Am. Chem. Soc.*, **52**, 206 (1930).

²¹⁸ Svrbely and Warner, *ibid.*, **57**, 655 (1935).

²¹⁹ McGowan, *Chemistry & Industry*, 607 (1936).

²²⁰ Zwecker, *Ber.*, **69**, 993 (1936).

²²¹ Hammett, *J. Am. Chem. Soc.*, **59**, 96 (1937).

²²² Fieser and Fieser, *ibid.*, **57**, 491 (1935).

²²³ Fry, *Z. physik. Chem.*, **76**, 385 (1911).

²²⁴ Stieglitz, *J. Am. Chem. Soc.*, **44**, 1299 (1922).

out parallel among aliphatic compounds. Also unexplained was the unique position of the halogens, which deactivate the ring while the other *ortho-para* directing substituents activate it.

The dualistic approach of Flürscheim and of Vorländer was more flexible. They superposed the idea of a general, non-alternating electrical polarity upon the older idea of an independent, alternating "valence demand," or "affinity capacity," whose relationship to electrostatic phenomena could not be traced.* The attempt to account for the apparent simultaneous production of alternating polarities around the benzene ring and a non-alternating effect has been the task of modern electronic theories.

During the last twenty years this problem has been attacked through a theoretical approach contributed to largely by Lapworth, Robinson, and Ingold.† These theories were approached purely from the direction of organic evidence. They advanced gropingly and with a rapidly expanding special nomenclature. They have been more successful than their predecessors in that their basic ideas have been independently derived by quantum mechanics and confirmed by modern physical methods of investigating molecular structure.

The most directly useful of these physical methods is the determination of dipole moments, and it is this method which has established the fundamental nature of the alternating and non-alternating electrostatic effects of groups. This study has confirmed the belief that in a bond between unlike atoms the electrons are on an average nearer one atom than another. The measurement of these displacements has taken the guesswork out of the assignment of electrical inductive effects to groups.‡ It is possible, in saturated compounds, to designate quantitatively the fractional part of an electronic charge which resides on each atom. It is found that all the common functional groups in neutral saturated compounds tend to attract electrons at the expense of carbon. Such a group at the end of a saturated chain will cause a general deficiency of electrons throughout the chain, rapidly damped but with no alternation in charge. These "inductive" effects are responsible for many chemical phenomena, such as the influence of substituents upon the dissociation constants of acids, but inductive effects do not divide the substituent

* For a review of these older theories, see Henrich, "Theories of Organic Chemistry," translation of 4th edition by Johnson and Hahn, John Wiley & Sons, New York (1922), pp. 175-236.

† For reviews see Robinson, "Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions," Institute of Chemistry of Great Britain and Ireland (1932); Ingold, *Chem. Rev.*, **15**, 225 (1934).

‡ For a review of the early contributions of dipole moment study to organic chemistry, see Sidgwick, "The Covalent Link in Chemistry," Cornell University Press (1933) Chapter 5.

groups into the right classes to provide a complete explanation of aromatic substitution. They are often overshadowed by effects of resonance, which were discovered as follows.

Every attempt to isolate isomers which differ only in the arrangement of bonds or electrons, while having identical positions of all the atoms, has resulted in failure. An important example is provided by the two *o*-xylene structures of Kekulé (pp. 121, 135). This failure has often been attributed to excessive stability of the one or the other form, or (as in the case of the *o*-xylenes) to very rapid interconversion between them. According to all recent physical studies of molecular structure (Chapter 26), such isomers cannot exist separately except in the rare event of their having different numbers of unpaired electrons. Instead, if a molecule can be represented in two or more electronic or bond structures, without moving any atoms, then the molecule will show characteristics of all such structures, and no one of them can exist independently of the others. This is the principle of resonance. If a molecule may have two exactly equivalent bond structures, then the molecule resembles one of these structures as much as the other, but is more stable than either alone would be by a large "resonance energy." The typical example of this is benzene, whose two Kekulé bond structures have identical energies. If benzene is a resonance hybrid, and not a mixture of tautomers, two physical methods should give evidence of this. In the first place, since single and double bonds between carbon atoms have the characteristic lengths 1.54 and 1.34 Å, respectively, x-ray¹² and electron diffraction²²⁵ studies of benzene should show such distances for Kekulé molecules. It is certain that there are no C—C distances in benzene as great or as small as these limits. The electron diffraction pattern of benzene is indistinguishable from that of a regular hexagon 1.39 ± 0.02 Å on a side, although the method is not sensitive enough to detect deviations from regularity of the order of a few hundredths of an Ångström unit. The vibrations of benzene as revealed in its infra-red, Raman, and fluorescence spectra are considered to be compatible only with complete hexagonal symmetry.²²⁶

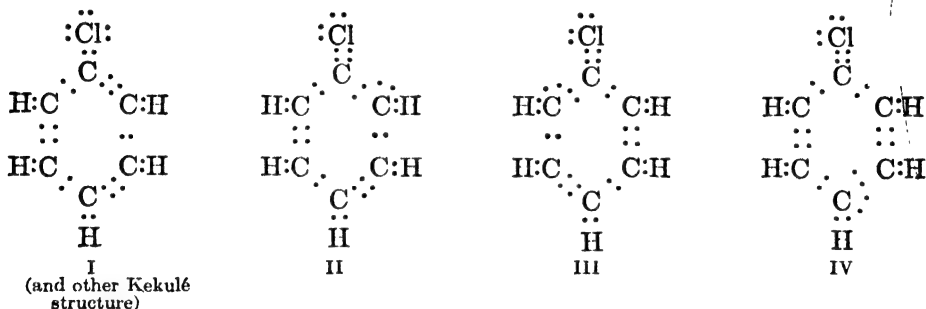
The chemical reactions of a resonance hybrid, unlike its physical properties, do not register the permanent state of the molecule, but only those states which are developed on the approach of a reagent. For example, if ozone enters into reaction with one of the bonds of *o*-xylene, resonance between Kekulé forms becomes impossible from that moment, and in the process of reaction two other double bonds are frozen in the corresponding cyclohexatriene positions. Since ozone may be expected

²²⁵ Schomaker and Pauling, *J. Am. Chem. Soc.*, **61**, 1770 (1939).

²²⁶ Ingold, *Proc. Roy. Soc.*, **A169**, 149 (1938).

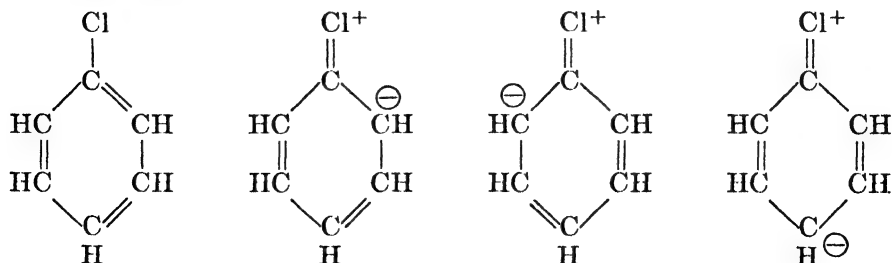
to attack that bond of *o*-xylene which already most resembles a double bond, the formation of both diacetyl and methylglyoxal may be taken to indicate that both Kekulé forms contribute importantly to the structure, although these forms have separate existence only during the course of being destroyed. It is found most useful to describe the course of aromatic reactions largely in terms of individual Kekulé bond structures, but such a structure is best regarded as something developed during the attack of the reagent.

Often two or more bond structures can be written, both of them satisfying the criterion of electronic octets, but differing largely in their chemical probability. An example of this is found in chlorobenzene



Here the principle of resonance still demands that the first structure shall not be independent of the second, third, and fourth, but it does not tell how important the contribution of the secondary structures will be. The higher their potential energy in comparison to the normal structure (the less their probability), the smaller their contribution to the true structure of the molecule will be and the less the resonance energy. Both these quantities may approach zero if the secondary structures are sufficiently improbable, without permitting a sharp dividing line between resonating and non-resonating systems. There are also many cases, such as that of naphthalene (p. 148) or urea, in which most of the chemical reactions are those normal for a single-bond structure, but where methods of studying the resting state of the molecule indicate substantial (though subordinate) contributions from secondary forms.

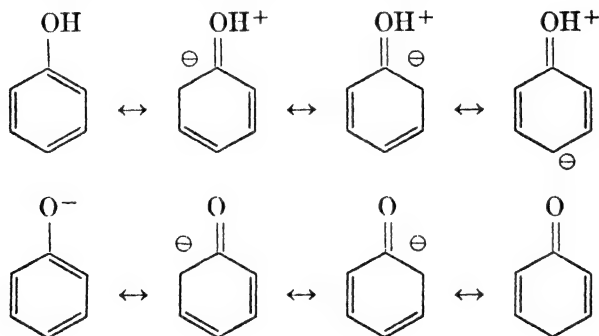
For purposes of discussion it is preferable to translate the electronic structures I-IV into bond structures



The question whether these secondary forms contribute appreciably to the structure of chlorobenzene must be answered by experiment. Among the physical evidence pointing to a detectible amount of resonance is the fact that aromatic halogen compounds (in common with vinyl halides) have markedly diminished electric moments compared to saturated halogen compounds;²²⁷ they also show a shortening of the C—Cl bond²²⁸ suggestive of double-bond character. On the organic side, such resonance provides interpretation of the diminished reactivity of halogen attached to the aromatic ring and of the directive influence of halogens in addition reactions to vinyl halides and in aromatic substitution.

Phenols, phenol ethers, and amines are the other common aromatic compounds which are capable of this type of resonance by virtue of having unshared electrons on the first atom of the substituent. The evidence of sharply altered dipole moments in comparison to aliphatic analogs is here even more striking than in chlorobenzene. In addition an interpretation is afforded of the acidity of phenols (and enols), the weakness of aromatic amines as bases (compare p. 212), and the directive power and extreme activating influence of the hydroxyl and amino groups.

A phenol and its anion are both capable of resonance with structures having negative charges in the *ortho* and *para* positions



In the phenol these secondary structures involve a separation of electric charge, which might be expected to oppose their occurrence, as in chlorobenzene. In the anion, however, this separation of charge is absent, and the secondary forms must therefore contribute more and make the resonance energy higher in comparison to the neutral phenol. This is a factor favoring the ionization equilibrium which is lacking in the acidic ionization of an alcohol.*

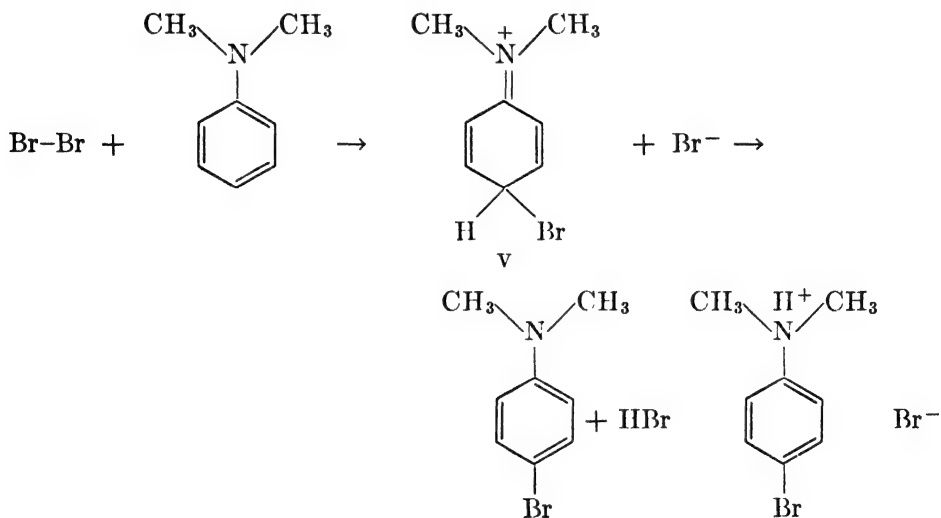
²²⁷ Sutton, *ibid.*, **A133**, 668 (1931); *Trans. Faraday Soc.*, **30**, 789 (1934).

²²⁸ Brockway and Palmer, *J. Am. Chem. Soc.*, **59**, 2181 (1937).

* The resemblance of these bond structures to those of keto-enol tautomers led to the original designation "tautomeric effect" by Robinson, who postulated such intramolecular tendencies long before the principle of resonance was enunciated. This term was not intended to imply a true tautomerism.

A similar analysis applied to the ionization of the dimethylanilinium ion shows that resonance makes it a stronger acid, and dimethylaniline itself therefore a weaker base, than in the case of a similar saturated amine.

With regard to the ease and orientation of aromatic substitution the Robinson-Ingold theory adopts the postulate, common to earlier theories, that the reagents which bring about substitution function as electron acceptors, and hence react preferentially at the points of high electron density in the nucleus. With a few reagents, such as mercuric acetate and the benzenediazonium ion (see p. 192), this electron-seeking character is obvious. It is not obvious in the case of molecular halogens that a halogen atom will enter the ring bearing a positive charge, and yet there is experimental evidence that the addition of halogen to an aliphatic double bond takes this course.²²⁹ It is assumed that the other common reagents yield substitution by paths similar to these. The bromination of dimethylaniline is represented



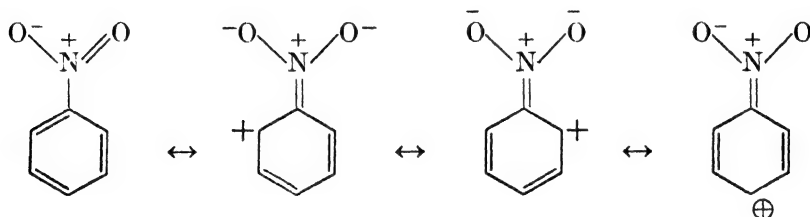
Pfeiffer and Wizinger¹⁶¹ have developed aliphatic analogies to this process. The choice of the *para* (or *ortho*) position is conditioned by two facts: (1) that it is already a center of excess negative charge, due to the resonance in the amine molecule; and (2) that an easy reaction path is available because the quinol-like transition state V (also capable of resonance with three other bond structures) is able to accommodate the positive charge long enough for a carbon-bromine bond to be formed and the carbon-hydrogen bond to be broken. The possibility of a certain amount of stabilizing resonance in the transition state as depicted

²²⁹ Bartlett and Tarbell, *ibid.*, **58**, 466 (1936); Tarbell and Bartlett, *ibid.*, **59**, 407 (1937)

also helps to explain why aromatic substitution proceeds by this path rather than by way of completed addition to one of the double bonds of the ring. The latter mechanism would eliminate so much stabilizing resonance as to constitute a very difficult path of reaction.

In the halobenzenes a transition state of a form like V offers a better reaction path than one involving attack of the bromine in one of the *meta* positions. Nevertheless, in the resting state of the molecule the normal form of chlorobenzene is so much more important than the secondary forms that the chlorine is still the strongly negative end of a dipole and all positions of the ring are deficient in electrons compared to benzene. This is the explanation given of the simultaneous deactivation and *ortho-para* directive influence of the halogen atoms.

Any group whose net effect is to make electrons permanently less available at the *ortho* and *para* positions must be not only deactivating, but also *meta* directing. This is true of the trimethylanilinium ion, the nitro, sulfonyl, nitrile, and carbonyl groups. Any drift of electrons toward C₁ brought about by an inductive effect will be at the expense of carbon atoms 2, 4, and 6, leaving atoms 3 and 5 relatively less affected. The situation is especially clear when resonance is possible, as in the nitro group



If these secondary structures are of any importance in the molecule then only the *meta* positions will have enough electron density to make a reaction with the usual reagents possible. The *ortho* and *para* positions should prove inviting points of attack for electron-donor reagents, and reaction is indeed observed at these positions in the formation of *o*-nitrophenol from potassium hydroxide and air,²³⁰ the reaction of trinitrobenzene with hydroxylamine to give picramide,²³¹ and similar reactions.

In certain substitution processes apparently proceeding through free radicals²³² the usual orientation rules are not applicable. The electronic theory of substitution has given little attention to this case.

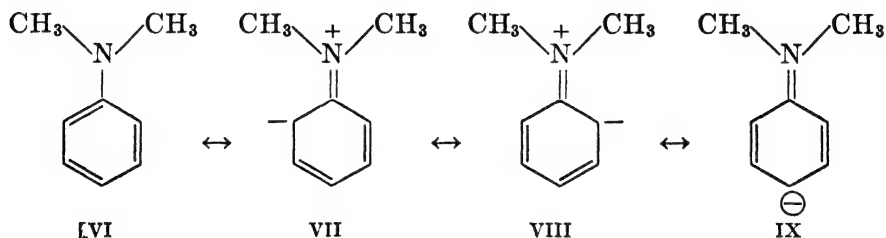
A stereochemical consequence of resonance, first pointed out by

²³⁰ Wohl, *Ber.*, **32**, 3487 (1899).

²³¹ Meisenheimer and Patzig, *Ber.*, **39**, 2534 (1906).

²³² Hey and Waters, *Chem. Rev.*, **21**, 178 (1937).

Birtles and Hampson,²³³ has helped to explain a puzzling case of steric hindrance commented upon earlier in this chapter. Since resonance is possible only between structures having the atoms in the same positions, it follows that the spatial arrangement of the atoms in nitrobenzene must be compatible with all the resonating bond structures. This means that all the atoms attached to double-bonded atoms must lie in the same plane, or the resonance will be damped. Similar considerations apply to dimethylaniline.

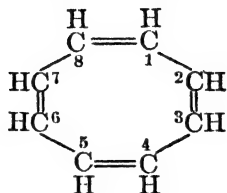


Although the form VI might have free rotation about the C—N bond, the forms VII, VIII, and IX must be coplanar, and therefore the molecule will remain coplanar at all times if these make any important contribution to its structure. If now a nitro or a methyl group is present in the *ortho* position, this coplanar arrangement becomes untenable on account of the steric interference of the groups. Anything which forces the dimethylamino group out of the plane of the ring damps the resonance and the effects resulting from the resonance may be expected to disappear. These include: (1) the special electric moment associated with aromatic amines, (2) the activation of the *ortho* and *para* positions toward substitution, and (3) the activation of the *ortho* and *para* hydrogen in condensation and exchange reactions. Hampson and his co-workers have found striking dipole-moment effects of this sort. The anomalous boiling points of the hindered methylanilines¹⁹⁶ may well be related to such reduced polarities. The remarkable inhibition of the diazo coupling reaction when a methyl group is *ortho* to a dimethylamino (but not to a monomethylamino) group is discussed on p. 197. An inhibited deuterium exchange in deuterio-alcohol has been found for similar cases by Brown, Kharasch, and co-workers.²³⁴ It is noteworthy in all these results that the damping of resonance is not absolute, even when conditions are imposed upon the molecule which are sterically very unfavorable to some of the bond structures.

²³³ Birtles and Hampson, *J. Chem. Soc.*, 10 (1937); Ingham and Hampson, *ibid.*, 981 (1939).

²³⁴ Brown, Kharasch, and Sprowls, *J. Org. Chem.*, **4**, 442 (1939); see also Brown, Widiger, and Letang, *J. Am. Chem. Soc.*, **61**, 2597 (1939).

In the light of damped resonance it is not to be expected that cyclo-octatetraene (p. 129) will show the stability of an aromatic compound. In order to exist without strain the molecule must take a puckered form in which carbon atoms 1, 4, 5, and 8 lie in an upper plane and carbon atoms 2, 3, 6, and 7 occupy a lower plane. This preserves all bond angles at their normal value and brings atoms 1, 2, 3, and 4 all into one plane,



atoms 3, 4, 5, and 6 all into another plane, etc. Any such spatial arrangement is incompatible with the alternative placing of the double bonds, for atoms 2, 3, 4, and 5 are not in a single plane, nor is any other sequence of four atoms in a position favorable to the second Kekulé structure. Resonance must then be damped severely unless the molecule adopts a coplanar arrangement, and this would involve angular strain.

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CHAPTER 4

STEREOISOMERISM

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PART I. INTRODUCTION

✓ / The term "isomers" is generally applied to those compounds which have the same molecular formula, but which differ in at least one of their physical or chemical properties. In terms of the structure of the molecule, this means that isomers differ in the arrangement of the atoms in the molecule. In fact, it has been the existence of many types of isomerism, especially of carbon compounds, which has been the chief reason for the extensive developments in attempts to represent the spatial arrangements of the atoms. The fundamental purpose of such structural models of molecules is to express as completely as possible the chemical and relative physical properties of the compound. For completeness, and to show all the types of isomerism exhibited by organic compounds, the following classification summarizes the present status of this division of theoretical organic chemistry.

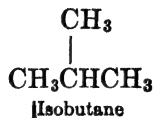
- (1) *Simple Structural Isomerism*. The difference between the isomers in this group can be adequately expressed by *simple structural formulas*.

- (a) *Nucleus or Chain Isomers*: compounds whose isomerism is due to the arrangement of the *carbon* atoms.

Examples:



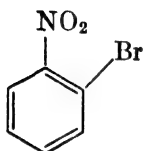
n-Butane



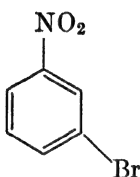
- (b) *Position Isomers*: compounds which differ in the position occupied by a group with reference to the carbon nucleus.

Examples:

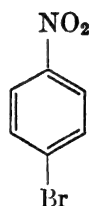
Cl



o-Bromonitrobenzene



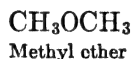
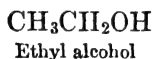
m-Bromonitrobenzene



p-Bromonitrobenzene

- (c) *Functional Group Isomerism*: compounds possessing the same molecular formulas but having different functional groups; i.e., belonging to different homologous series.

Examples:



Tautomers constitute a special case of functional group isomerism. They are isomers which are *directly* and *readily* interconvertible.

Example:

O

OH



Acetoacetic ester



- (2) *Stereoisomerism or Space Isomerism*. Isomers possessing the same molecular formulas and the same functional groups but which differ in the *three-dimensional space arrangement* of the atoms or groups within the molecule are said to be stereoisomers. >

The discussion in the following sections will be limited to a consideration of the fundamental concepts of the two common types of stereoisomerism which are:

(a) Optical isomerism.

(b) *cis-trans* Isomerism (geometrical isomerism).

PART II. OPTICAL ISOMERISM. GENERAL THEORY

RALPH L. SHRINER and ROGER ADAMS

Optical Activity

✓ Experimentally it has been observed that only certain substances, both organic and inorganic, possess the power of rotating the plane of polarized light (p. 282). Examination of the nature of these optically active compounds has shown that only those structures (crystalline or molecular) which possess mirror images not superimposable upon the original are able to affect plane-polarized light. Such compounds are generally termed *asymmetric* because their structure is without complete symmetry from a geometrical standpoint.) This requirement for optical activity will become clearer as the discussion progresses. Optically active substances may be divided into two classes depending upon whether activity is due to crystal structure or to molecular structure.

Optical Activity Due to Crystal Structure. A familiar example of this type is quartz, which is found to exist as *dextro* and *levo* rotatory crystals, commonly known as *d*- and *l*-forms. X-ray examination of these quartz crystals has shown that the crystal lattice is built up of silicon and oxygen atoms so arranged that a spiral staircase effect is obtained. The mirror image of this crystal lattice is not identical with it, and hence the *crystal* is asymmetric and rotates plane-polarized light.

Optically active crystals, such as quartz or sodium chlorate, are often hemihedral, and the crystals themselves are mirror images of each other. This relationship is not always true, since many optically active crystals show no trace of hemihedral faces. Optical activity has been observed in isotropic, uniaxial, and biaxial crystals. Table I lists some of the compounds which are optically active in the crystalline state *only*.

TABLE I

| ISOTROPIC CRYSTALS | UNIAXIAL CRYSTALS | BIAXIAL CRYSTALS |
|-----------------------|----------------------|-------------------|
| Sodium chlorate | Quartz | Hydrazine sulfate |
| Sodium bromate | Cinnabar | Barium formate |
| Sodium uranyl acetate | Potassium dithionate | Iodic acid |
| Sodium sulfantimonate | Benzil | Zinc sulfate |

Crystals of many other compounds also exhibit optical activity, but all substances in this group lose their activity when fused or dissolved in a solvent.

Optical Activity Due to Molecular Structure. Optically active compounds in this group rotate the plane of polarized light, regardless of the physical state. Optical activity is exhibited by solutions of the compound, as well as by the pure compound in the crystalline, liquid, or gaseous state. In a few compounds the crystals may possess hemihedral faces and be mirror images of each other, but this relationship between crystals is not universally true. The optical activity must hence be ascribed to, and be dependent upon, *the structure of the molecule*.

✓ Principles of Molecular Asymmetry

✓ Molecules with spatial arrangements of their atoms which are asymmetric may exist in optically active forms. As mentioned above, the configuration of such a molecule is characterized by the fact that it is not identical with its mirror image. The molecule and its mirror image are frequently called *enantiomorphs* and are identical with each other in their chemical and physical properties except in the rotation of plane-polarized light. The optical activity is the same in degree but opposite in sign.) It is relatively simple to determine from the structural model of a molecule whether a non-identical mirror image is possible.

The above statements are very general and cover all cases in which optical activity is due to the structure of the molecule. For purposes of discussion it is convenient to divide such asymmetric molecules into two groups.

1. Compounds in which an individual atom is asymmetric.
2. Molecules containing no individual asymmetric atoms.

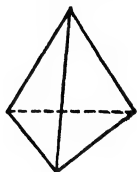
Their asymmetry is due to the absence of any of the necessary elements of symmetry which permit the mirror image of the molecule to be superimposable.

Many examples of both types are known. The largest number is found in the first group in which the asymmetric atom is carbon, but other atoms may also give rise to optical isomers. The three-dimensional space model is evidently dependent upon the directional distribution of the valence forces of these atoms.

✓ Spatial Arrangements of Valencies of Atoms

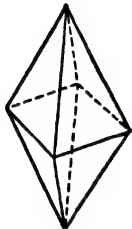
The study of the physical and chemical properties of the stereoisomers of compounds of twenty-three elements has led to the conclusion that the distribution of valencies is tetrahedral, octahedral, or planar.

Group I. Tetrahedral Configuration.



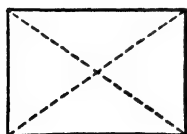
Be, B, C, N, Si, P, S, Cu, Zn, As, Se, Sn,
Te, Ge, Pt, Pd.

Group II. Octahedral Configuration.



Al, Cr, Fe, Co, Zn, As, Rh, Ru, Ir, Pt.
(Cu, Ni?)

Group III. Planar Configuration.



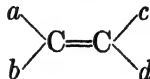
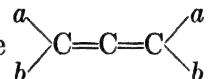
Ni, Pt, Pd.

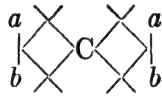
Of all the elements investigated, carbon has been the most exhaustively studied. In 1874 Le Bel and van't Hoff independently and simultaneously proposed that the four valencies of carbon in its compounds were distributed in three dimensions. van't Hoff regarded the valence bonds as equidistant from each other and so arranged that a regular tetrahedron resulted by joining the ends of the valence bonds by straight lines. Le Bel on the other hand did not consider that the carbon atom had such a rigid structure. The experimental evidence of the past sixty-eight years has fully confirmed their hypothesis although the idea of a perfectly tetrahedral model with the four valencies absolutely fixed in a rigid position, at angles of $109^{\circ} 28'$ apart, has undergone some modification.

Evidence for the Tetrahedral Carbon Atom

1. The four valencies of carbon are identical.
2. A consideration of all types of isomerism of carbon compounds on the basis of a planar, pyramidal, and tetrahedral configuration of the carbon atom has shown that *only* the tetrahedral is consistent with *all* the facts. Thus, a planar or pyramidal configuration calls for two

geometrical isomers of compounds of the type Ca_2b_2 ; a pyramidal configuration calls for optical isomers of Ca_2bc ; no such isomers are known. In the case of $Cabcd$ only two optical isomers are known.

3. Ethylenic compounds with the structure  exhibit geometrical isomerism but *not* optical isomerism (p. 446). Allenes with the structure  give rise to optical isomers and not geometrical isomers.

4. Spiranes of the type  are resolvable into *d*- and *l*-forms. If the carbon atom were planar or pyramidal no resolution would be possible.

5. No cases of stereoisomerism due to the acetylenic linkage are known.



6. The chemistry of carbon rings, their formation, stability, strainless rings, double and triple bonds in rings—all these are consistent only with the tetrahedral arrangement (p. 68).

7. The measurements of dipole moments (p. 1752) have served to confirm the above chemical evidence from the physical side. Thus, in the series of simple halogenated methanes given below, the perfectly symmetrical molecules, methane and carbon tetrachloride, have moments of zero.

| | | | | |
|-----------|------------------------------|-----------------------------|------------------------------|-----------|
| CH_4 | CH_3Cl | CH_2Cl_2 | $CHCl_3$ | CCl_4 |
| $\mu = 0$ | $\mu = 1.85 \times 10^{-18}$ | $\mu = 1.6 \times 10^{-18}$ | $\mu = 1.05 \times 10^{-18}$ | $\mu = 0$ |

The other three have an unequal distribution of mass and electrostatic charges about the central carbon atom and hence possess definite dipole moments.

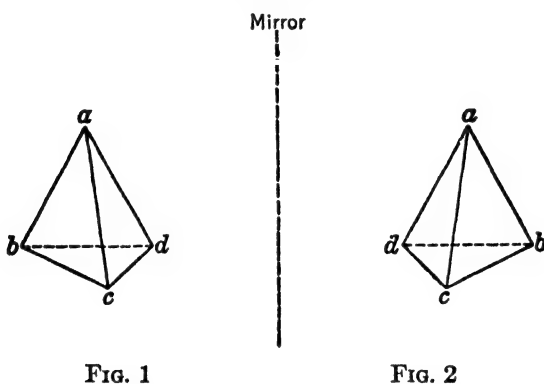
8. The structure of many complex cyclic, bicyclic, and tricyclic compounds requires a tetrahedral carbon atom in constructing the models of such molecules. Planar or pyramidal carbon atoms would not permit the construction of such models without involving enormous strains.

The evidence concerning tetrahedral, octahedral, and planar configurations of the other elements will be considered in Part IX.

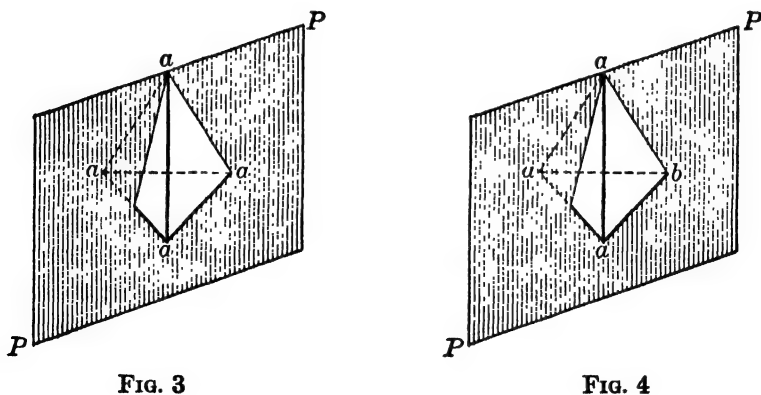
PART III. OPTICAL ISOMERISM OF COMPOUNDS CONTAINING ASYMMETRIC CARBON ATOMS

✓ Molecules Containing One Asymmetric Carbon Atom

General Concepts. Using the tetrahedral model of the carbon atom it is easily observed by means of the structural models that a compound containing a carbon atom attached to four different groups, $Cabcd$, possesses a mirror image which cannot be superimposed on the original (Figs. 1, 2). Such a molecule is asymmetric, and hence a carbon atom of this type is called an *asymmetric carbon atom*.



One of the means used to decide whether or not a molecule is asymmetric is to determine the presence or absence of a plane of symmetry in the molecule. A *plane of symmetry* is one that will divide a molecule into



halves, each of which is the mirror image of the other.) It is clear by examining the models of the compounds Ca_4 , Ca_3b , Ca_2bc , and Ca_2b_2 (Figs. 3, 4, 5, 6) that all of them possess a plane of symmetry (PP).

The mirror images of the models represented by Figs. 3, 4, 5, 6 are identical with the originals, and no optical isomerism is possible. The experimental facts observed on compounds with structures correspond-

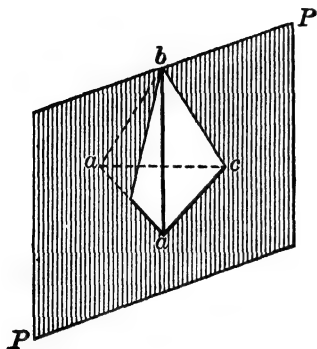


FIG. 5

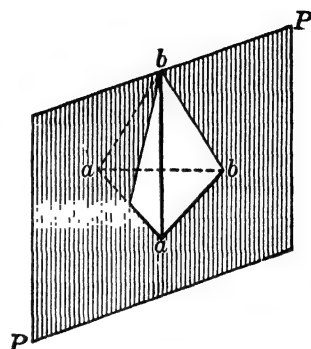


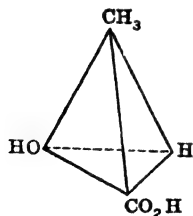
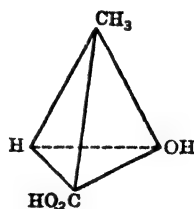
FIG. 6

ing to these type formulas confirm these theoretical predictions. The molecule represented by Fig. 1 possesses no plane of symmetry, and may exist in two optically active forms, a *dextro* and a *levo* form, represented by Figs. 1 and 2. If equal amounts of the two isomers, *d*- and *l*-, are mixed together, the optical effect of each form is neutralized by the other and a product is obtained which is known as a *racemic modification*.

Historically, lactic acid was one of the first compounds examined. It was found to exist in:

1. An inactive form—racemic lactic acid.
2. A *dextrorotatory* form—sarco-lactic acid.
3. A *levorotatory* form—fermentation-lactic acid.

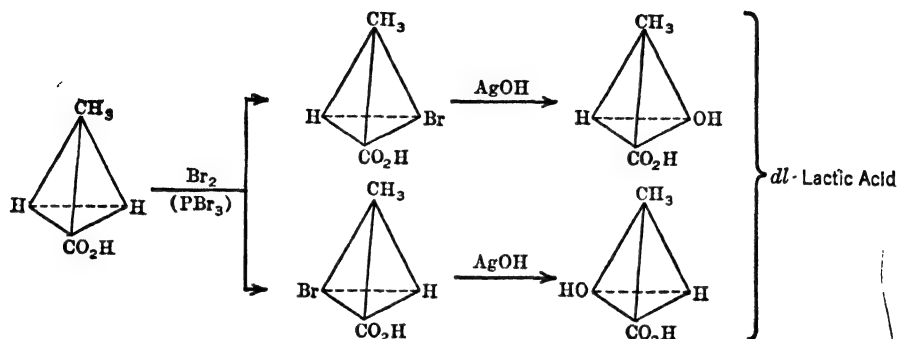
The models of lactic acid are represented in Figs. 7 and 8.

FIG. 7
d-Lactic acidFIG. 8
l-Lactic acid

Inactive or racemic lactic acid (*dl*-Lactic acid)

The biological processes in living muscle produce *d*-lactic acid (Fig. 7), the action of certain microorganisms on lactose forms *l*-lactic acid (Fig. 8), and the laboratory synthesis of lactic acid leads to an equi-

molecular mixture of *d*- and *l*-forms which constitutes the inactive modification known as racemic lactic acid (*dl*-lactic acid). The following reactions represent one possible synthesis.



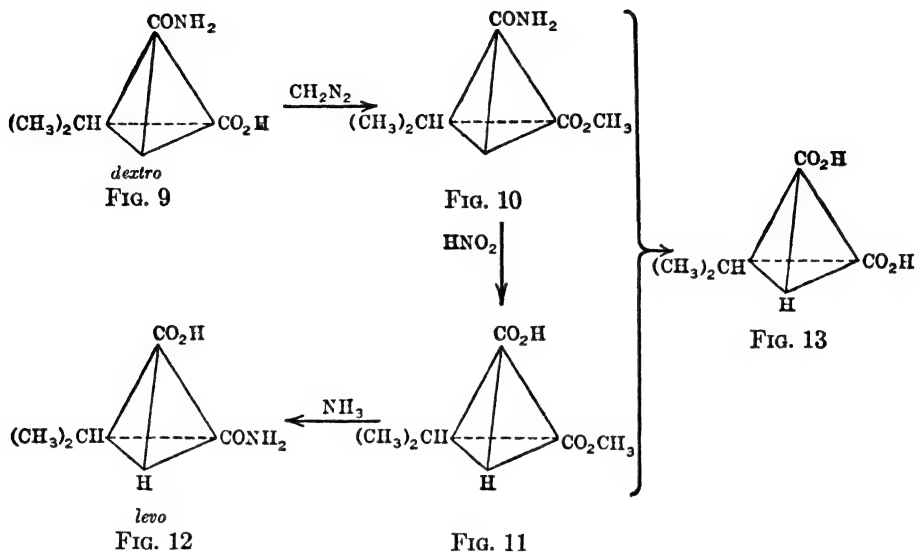
The starting molecule, propionic acid, cannot exist in optically active forms, since it has a plane of symmetry. In the bromination reaction either of the two α -hydrogen atoms may be replaced by bromine producing *d*- and *l*- α -bromopropionic acids in equal amounts, since the two hydrogens are similarly situated in the molecule. The probability of obtaining the *d*-form is hence equal to the probability of obtaining the *l*-form, and therefore, racemic or *dl*- α -bromopropionic acid results. The reaction with silver hydroxide must produce *dl*-lactic acid from the *dl*- α -bromopropionic acid.

Examination of the general formulas in Figs. 1 and 2 shows that if any two groups are interchanged in one model the resulting structure will be identical with the mirror image of the original. Thus, exchanging the positions occupied by *a* and *b* (or any other two groups, *a* and *c*, *a* and *d*, *b* and *c*, *b* and *d*, or *c* and *d*) in Fig. 1 gives a model identical with Fig. 2. Such an exchange was accomplished experimentally by Emil Fischer, who thus demonstrated conclusively that the relationship between optical isomers must be due to spatial factors and not to any structural factors. The reactions, Figs. 9–12, demonstrate the interchange of the carboxyl and amide groups.

Other experiments have also readily demonstrated that reactions which made two groups attached to the originally asymmetric carbon atom identical resulted in optically inactive products. Thus, the hydrolysis of any of the four compounds above leads to the isopropyl malonic acid (Fig. 13) which is inactive and cannot exist in optically active forms (*cf.* Fig. 5).

For many years all the known optically active compounds of carbon contained two or more carbon atoms in the molecule. As a consequence, there arose the question whether factors, other than the presence of an

asymmetric carbon atom, were necessary for optical activity in a molecule. However, in 1914 Pope and Read established the fact that a



single carbon was all that was necessary, provided that it was asymmetric. The resolution of chloriodomethanesulfonic acid into its optical enantiomorphs (Fig. 14) was accomplished.

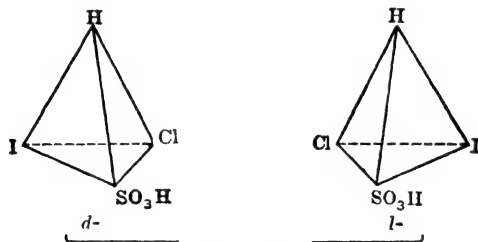


FIG. 14

Properties of Enantiomorphs. Within the limits of experimental error all the physical properties of the *d*- and *l*-forms of a compound are identical except the effect on plane-polarized light. In respect to their optical rotatory power, each isomer rotates the plane of polarized light exactly the same number of degrees but in opposite directions. No other distinctive differences between optical isomers which are mirror images of each other have ever been noted.* The crystal forms of enantio-

* Claims have been made that differences between the *d*- and *l*-forms exist. (See Campbell, *J. Am. Chem. Soc.*, **53**, 1661 (1931).) The differences are within the experimental error of the observations and the degree of purity of the materials.

morphs may also be mirror images of each other, but this relationship of the crystals is unusual.

Since optical isomers contain the same atoms and groups in the same relationship to each other (although in a different spatial order), their chemical reactions are identical. In a reaction with another optically active molecule, the *d*- and *l*-forms may react at different rates, but the type of reaction is identical.

Studies on the physiological effects of optical isomers have shown that there may or may not be considerable differences between the *d*- and *l*-forms. Where one optically active isomer exhibits a specific difference it seems probable that diastereoisomers are produced by the reaction of the optically active agent with some optically active component of the living tissue. Such diastereoisomers have different properties and hence would be expected to cause differing physiological action.

The properties of racemic modifications will be discussed later (p. 248). Generally the racemic forms differ in many respects from the optically active isomers.

Principle of Free Rotation. Ethane exists in only one form. This means that the two carbon atoms in ethane (Fig. 15) and its derivatives must be able to rotate with reference to each other about the single bond joining the two together. For example, lack of free rotation in ethylene

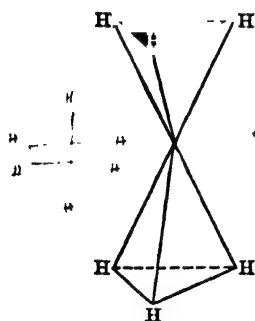


FIG. 15

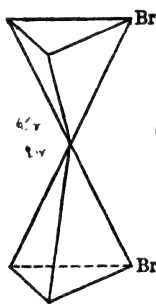


FIG. 16

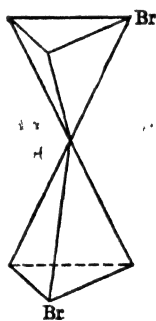


FIG. 17

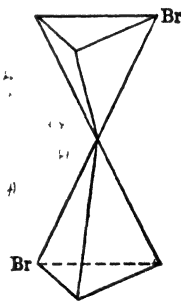


FIG. 18

bromide would indicate an indefinite number of isomers. Figures 16, 17, and 18 represent three such possibilities. Since the number of isomers agrees with the idea that the carbon atoms are free to rotate, this principle has been accepted as holding true for all simple molecules and must be kept in mind in considering structural formulas or models.

Certain types of molecules have been found in which atoms are joined by a single bond but are so substituted that the rotation is restricted or prevented. These molecules will be considered in Part VIII.

Compounds Containing Two Different Asymmetric Carbon Atoms

A substituted ethane of the general formula $Cabc-Cdef$ contains two different asymmetric carbon atoms, and construction of the models shows that four optical isomers corresponding to Figs. 19, 20, 21, and 22 should exist.

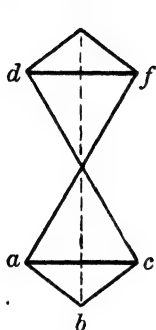


FIG. 19

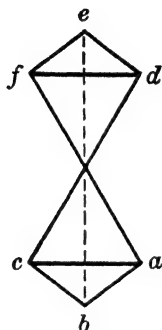


FIG. 20

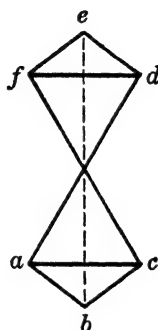


FIG. 21

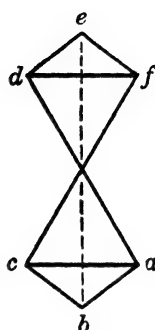


FIG. 22

Mirror-Image Relationship. Experiment fully justifies these models, and many cases are known in which all four optical isomers have been obtained. The relationship between the isomers is important. The molecule corresponding to Fig. 19 is the mirror image of that represented by Fig. 20. An equimolecular mixture of these two, therefore, constitutes a racemic modification. Similarly, the molecules represented by Figs. 21 and 22 would also constitute a racemic modification.

The relationship between the molecules represented by Figs. 19 and 21 is quite different. They are *not identical* and are *not mirror images* of each other. A careful examination of the two models shows that they differ in the spatial distribution of the groups. Thus, with the models in the position shown with group e above group b in both Figs. 19 and 21, it is clear that d is closer to a in Fig. 19 than in Fig. 21, and the same is true for groups f and c . For this reason, the molecules represented by Figs. 19 and 21 are called *diastereoisomers*.* Similarly, Fig. 19 is also a diastereoisomer of Fig. 22; Fig. 20 is a diastereoisomer of Fig. 21 or 22. However, no such differences in the distances between the groups exist in the models constituting the pair of mirror images. Thus, it should be noted that in Fig. 19 the group a is exactly the same distance from the other five groups as the group a in Fig. 20. In enantiomorphs, therefore, the groups bear the same space relationship

* The word diastereoisomer is derived from four Greek words: $\delta\acute{\iota}\alpha$, *through*; $\sigma\tau\epsilon\rho\epsilon\omicron\varsigma$, *solid or space*; $\acute{\iota}\sigma\omicron\varsigma$, *equal*; and $\mu\acute{\epsilon}\rho\omicron\varsigma$, *part*; isomers through space. The term diamer, a contraction of diastereoisomer, is also used, but this term resembles dimer so closely that it may lead to confusion.

to each other; the only difference is their arrangement. These diastereoisomeric relationships and the above-mentioned enantiomorphic relationships hold true, even though one carbon atom rotates with respect to the other.* The mirror-image relationship will exist at any point in the synchronous rotation of the mirror images.

Diastereoisomers differ from each other in physical properties, such as optical rotation, melting point, and solubility. Their chemical reactions are of the same type, since they possess the same functional groups, but the *rates* of reaction are different.

Notation. Various schemes of notation have been developed for representing these space models on paper. Figures 23, 24, 25, and 26

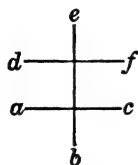


FIG. 23

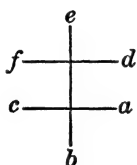


FIG. 24

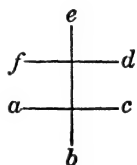


FIG. 25

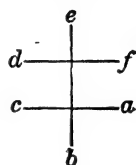


FIG. 26

indicate one method for representing the space models shown in Figs. 19–22. The asymmetric carbon atoms are understood to be present where the lines cross.† According to another scheme the top asymmetric carbon atom is represented by the capital letter *A* and the bottom one by *B*, and the *configurations* by plus, (+), and minus, (–), signs.‡ Figure 27 thus summarizes the number of isomers for a molecule with two different asymmetric carbon atoms.

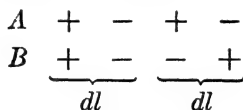


FIG. 27

Formation of a Compound Containing Two Different Asymmetric Carbon Atoms from a Compound Containing Only One Asymmetric Carbon Atom. As a specific example of this transformation the bromination by the modified Hell-Volhard-Zelinsky method of *dextro*- β -methylvaleric acid (Fig. 28) may be considered. The configurations of the two possible bromo acids are shown in Figs. 29 and 30.

* The student should satisfy himself that these relationships and statements are true by actual construction of the models.

† In using this system, it is important to visualize the positions of the groups relative to the plane of the paper. The groups *eb* are in the plane of the paper and the groups *acdf* are above the plane of the paper extending toward the observer. This is in accord with the Fischer convention. See Hudson, *J. Chem. Ed.*, **18**, 353 (1941).

‡ Care must be taken not to confuse the plus or minus signs with direction of rotation. The signs merely denote possible configurations.

The bromine may replace either of the two α -hydrogens in the *dextro* acid, resulting in the two optically active diastereoisomers represented by Figs. 29 and 30 in which the top asymmetric carbon atoms *A* have different configurations, but *B* has the same configuration as in the starting material. The important point to be noted in such a reaction is that the two diastereoisomers (Figs. 29, 30) are produced in *unequal*

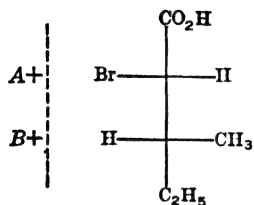
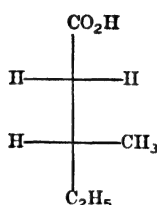


FIG. 29



dextro
FIG. 28

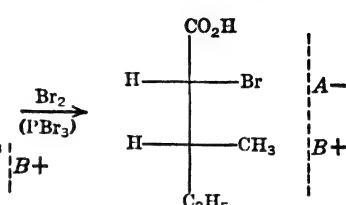


FIG. 30

amounts. This is due to the fact that in the *optically active* molecule (Fig. 28) the two hydrogen atoms bear different relationships to the groups about the asymmetric carbon atom *B*. Hence, they will react with the bromine at different rates, and at the end of any given time the two products (Figs. 29 and 30) will be present in unequal amounts. This production of diastereoisomers in unequal amounts is general for all such reactions. It is possible, of course, that equal amounts might result, but this would be purely fortuitous. Also, one reaction may proceed so rapidly that only one product is actually isolated.

In the same manner, the bromination of *levo*- β -methylvaleric acid (Fig. 31) produces the two diastereoisomeric bromo acids (Figs. 32, 33) in unequal quantities but in amounts inversely proportional to those obtained from the *dextro* isomer.

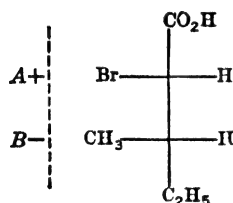
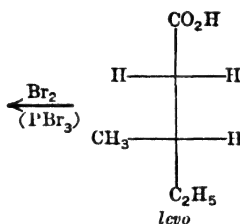


FIG. 32



levo
FIG. 31

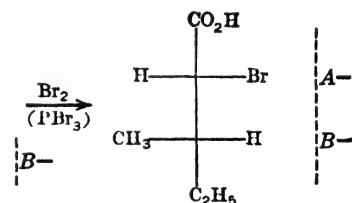


FIG. 33

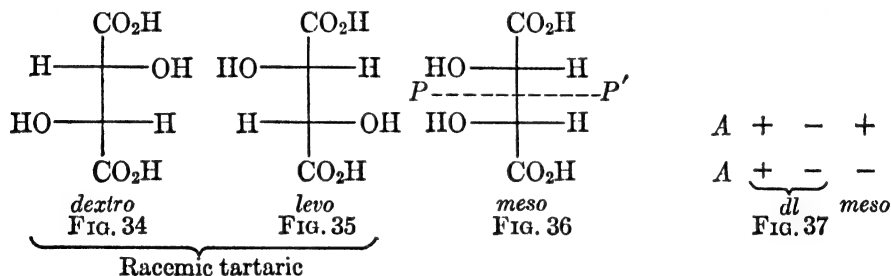
If the racemic modification of β -methylvaleric acid (consisting of 50 per cent *dextro*, Fig. 28, and 50 per cent *levo*, Fig. 31) is brominated, all four bromo acids will be produced. Owing to the fact that the α -hydrogen atoms in Figs. 28 and 31 have similar relationships, the molecules corresponding to Fig. 29 and Fig. 33 will be formed in equal amounts and constitute one racemic modification, and Figs. 30 and 32 constitute a

second racemic modification. The relative amounts of these racemic modifications will be different since their constituents bear a diastereoisomeric relationship to each other, as pointed out above. These two racemic modifications will have different physical properties and may be separated from each other by crystallization. In this connection, it should be recalled that enantiomorphs possess the same physical properties and cannot be separated by a process such as fractional crystallization.

These relationships are of fundamental importance, and must be thoroughly understood. Most asymmetric syntheses (p. 308) and the kinetic method of resolution (p. 260) ultimately rest upon the production of diastereoisomers in unequal amounts. The most important method of resolution of racemic modifications (p. 256) rests upon the differences in physical properties of diastereoisomers.

Compounds Containing Two Similar Asymmetric Carbon Atoms

The classical examples of molecules of this type are the isomers of tartaric acid, shown in Figs. 34, 35, and 36, and summarized in Fig. 37.



d-Tartaric acid is composed of two identical *dextrorotatory* carbon atoms, and the entire molecule is *dextro* (Fig. 34). Its mirror image, *l*-tartaric acid, is made up of two identical *levorotatory* carbon atoms, as shown in Fig. 35. The equimolecular mixture of the two constitutes the racemic modification.

Racemic and *meso*-Tartaric Acids. The molecule represented by Fig. 36 constitutes a new isomer. It is composed of one *dextrorotatory* carbon atom, and an exactly similar *levorotatory* carbon atom. Since the two asymmetric carbon atoms are exactly alike, but rotate the plane of polarized light the same number of degrees in opposite directions, the net rotation will be zero, and the molecule is optically inactive. This conclusion is confirmed by examination of the model, since it is clear that a plane of symmetry passes through the center of the molecule on the line *PP'*. This form is called *meso*-tartaric acid. It is optically

inactive by *internal compensation* as contrasted with *dl*-tartaric acid which is optically inactive by *external compensation*. There is only one *meso* form of tartaric acid since the compound obtained by exchanging the hydrogens and hydroxyl groups of Fig. 36 is identical with Fig. 36. This *meso* form is a diastereoisomer of the *d*- and *l*-tartaric acids and differs from them in physical properties. Some of these differences are shown in Table I.

TABLE I

COMPARISON OF PHYSICAL PROPERTIES OF THE FOUR TARTARIC ACIDS

| Property | <i>d</i> -Tartaric | <i>l</i> -Tartaric | <i>dl</i> -Tartaric (Compound) | <i>meso</i> - Tartaric |
|---|------------------------|------------------------|-----------------------------------|---------------------------|
| 1. Melting point..... | 170° C. | 170° C. | 206° C. | 140° C. |
| 2. Ionization— K_1 | 0.00117 | 0.00117 | 0.0011 | 0.00077 |
| 3. Ionization— K_2 | 0.000059 | 0.000059 | 0.000058 | 0.000016 |
| 4. Density..... | 1.76 | 1.76 | 1.687 | 1.666 |
| 5. Solubility (g. in 100 g. H ₂ O at 15°)..... | 139 | 139 | 20.6 | 125 |
| 6. Refractive index..... | | | 1.4246 | 1.4315 |
| 7. Specific rotation $[\alpha]_D^{25}$ (20 per cent solution H ₂ O)..... | +12 | -12 | Inactive | Inactive |
| 8. Dipole moments of diethyl esters..... | 3.12×10^{-18} | 3.12×10^{-18} | 3.16×10^{-18} | 3.69×10^{-18} |
| 9. Boiling points of di- ethyl esters..... | 157°/11 mm. | 157°/11 mm. | 157°/11.5 mm. 158°/14 mm. | 157.5°/14 mm. |

The data in Table I indicate that the *d*- and *l*-forms have the same physical properties except their effect on plane-polarized light. The *dl*- and *meso*-tartaric acids differ in physical properties from each other and from the *d*- and *l*-forms. The data on the diethyl esters are of interest since they indicate that the boiling points of the isomers are very close together (see footnote, p. 256). The dipole moments of the *d*-, *l*-, and *dl*-diethyl tartrates are identical (within experimental error), but that of the *meso*-diethyl tartrate is distinctly higher, which is further evidence for the configuration assigned to it.

Optically active molecules containing more than one asymmetric carbon atom have a rotation which is the algebraic sum of the rotations of the individual asymmetric atoms. The best evidence for this is the fact that the *meso* form is optically inactive.

Compounds Containing Three Different Asymmetric Carbon Atoms

The conversion of molecules with two different asymmetric carbon atoms into compounds with three different asymmetric carbon atoms is shown diagrammatically in Fig. 38, in which the arrows represent chemical reactions which generate a new asymmetric carbon atom different from the two already present.

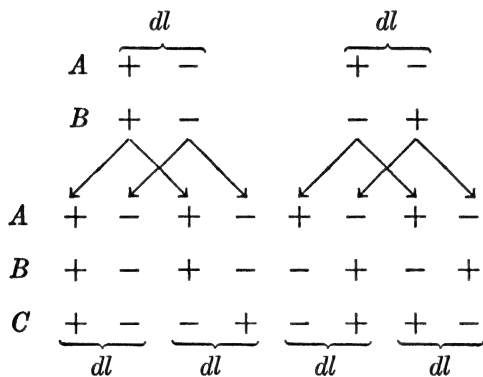


FIG. 38

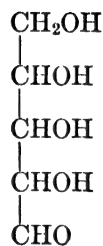


FIG. 39

There will be eight optical isomers existing as four racemic modifications. Any one isomer is a diastereoisomer of each of the others except its own mirror image. The aldopentoses (Fig. 39) constitute a specific example of this type, in which all the eight isomers are known.

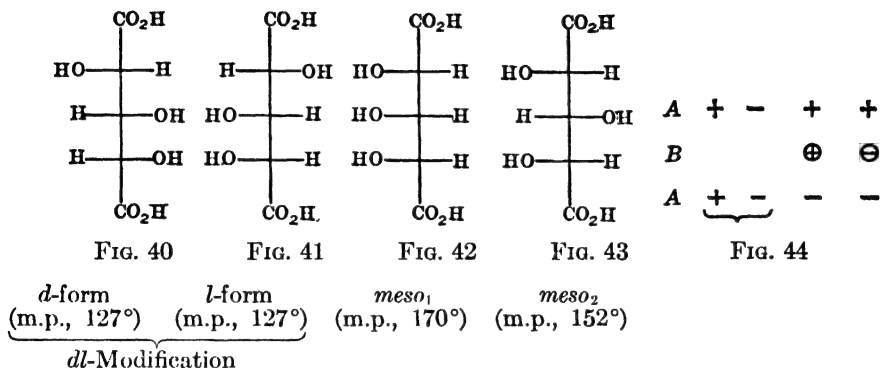
Each racemic form of the molecule containing two different asymmetric carbon atoms produces two racemic modifications of the compound with three asymmetric carbon atoms, and these two racemic forms will be produced in unequal amounts.

Compounds Containing Three Asymmetric Carbon Atoms, Two of Which Are the Same

The trihydroxyglutaric acids obtained by oxidation of the pentoses have been found to exist in the forms shown in Figs. 40, 41, 42, 43, and summarized in Fig. 44.

In the molecules corresponding to Figs. 40 and 41 the two end asymmetric carbon atoms (as in Fig. 44) are either both *dextro* or both *levo*, respectively. The entire molecules are mirror images of each other and constitute a racemic modification. In these models the central carbon *B* is *not* asymmetric, since two of the groups attached to it are identical. If, however, the two end asymmetric carbon atoms have opposite configurations, i.e., one *A* is *dextro* and the other *A* is *levo*, then *B* has four

different groups attached to it. The question therefore arises as to the effect such a carbon atom exerts on the molecule. Examination of the two models* corresponding to Figs. 42 and 43 shows that each possesses a plane of symmetry drawn through the central carbon atom and its hydrogen and hydroxyl groups. Hence, these molecules are not asymmetric and, therefore, cannot affect plane-polarized light. Experiments



with the trihydroxyglutaric acids have confirmed the fact that such molecules are *not* optically active, but are internally compensated or *meso* forms. Since, however, the central carbon can have two different configurations by exchanging the H and OH groups as shown in Figs. 42 and 43, there will be *two meso* forms.

A carbon atom of this type, although it holds four different groups, possesses a plane of symmetry because of the fact that two of these groups are mirror images of each other. It is, therefore, not *truly* asymmetric and hence is termed *pseudoasymmetric*. In order to distinguish such pseudoasymmetric carbon atoms in the notation shown by Fig. 44, they are represented by circles containing plus or minus signs.

Compounds Containing Four Asymmetric Carbon Atoms

The presence of four different asymmetric carbon atoms in a compound gives rise to sixteen optical isomers which can form eight racemic modifications. Figure 45 summarizes the possibilities for such molecules. The aldohexoses (Fig. 46) are molecules of this type. All sixteen isomers are known and well characterized.

In the special case of a molecule containing two pairs of similar asymmetric carbon atoms there will be only eight active forms existing

* The student should build up models corresponding to Figs. 40, 41, 42, and 43, using tetrahedral models, and observe the space relationships between these isomers.

as four racemic modifications and two additional *meso* forms. Figure 48 represents the isomers of the dibasic acids (Fig. 47) obtained by oxida-

| | | | | | | | | | | | | | | | | | |
|---|--------------------------------|---|--------------------------------|---|--------------------------------|---|--------------------------------|---|--------------------------------|---|--------------------------------|---|--------------------------------|---|--------------------------------|---|--------------------|
| | | | | | | | | | | | | | | | | | CH ₂ OH |
| A | + | - | + | - | + | - | + | - | - | + | + | - | - | + | + | - | CHOH |
| B | + | - | + | - | + | - | - | + | + | - | + | - | + | - | - | + | CHOH |
| C | + | - | + | - | - | + | + | - | + | - | - | + | + | - | + | - | CHOH |
| D | + | - | - | + | + | - | + | - | + | - | - | + | - | + | - | + | CHOH |
| | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | CHO |

FIG. 45

FIG. 46

tion of the primary alcohol and the aldehyde groups of the aldohexoses (Fig. 46) mentioned above.

| | | | | | | | | | | | | | | | | | |
|-------------------|---|--------------------------------|---|--------------------------------|---|--------------------------------|---|--------------------------------|---|--------------------------------|---|--------------------------------|---|--------------------------------|--|--------------------------------|-------------|
| CO ₂ H | | | | | | | | | | | | | | | | | |
| CHOH | A | + | - | + | - | + | - | + | - | + | - | + | + | | | | |
| CHOH | B | + | - | + | - | + | - | - | + | - | + | - | + | | | | |
| CHOH | B | + | - | + | - | - | + | - | + | + | + | - | - | | | | |
| CHOH | A | + | - | - | + | + | - | + | - | + | - | - | - | | | | |
| CO ₂ H | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | | $\underbrace{\quad\quad}_{dl}$ | |
| | | | | | | | | | | | | | | | | <i>meso</i> | <i>meso</i> |

FIG. 47

FIG. 48

Compounds Containing Five Asymmetric Carbon Atoms

Construction of the models of a molecule containing five different asymmetric carbon atoms shows that thirty-two optical isomers exist as sixteen racemic modifications. A study of the number of isomers found in compounds containing different asymmetric carbon atoms in a chain has shown that the number is equal to 2^n where n equals the number of asymmetric carbon atoms. This formula is used, therefore, to determine the number of isomers rather than building the models or drawing the possibilities by the *A*, *B*, *C*, *D*, *E* notation.

A molecule of the type *A-B-C-B-A* is interesting because of the question concerning the influence exerted by the carbon atom *C* on the properties of some of the isomers. A summary of the sixteen possible isomerides is shown in Fig. 49.

The isomers numbered 1, 2, 3, 4 constitute two racemic modifications. Since the ends of these molecules are identical, carbon *C* is not asym-

metric. In forms 5, 6, 7, 8 a plane of symmetry is present and the ends AB are mirror images of each other. Hence, C is now pseudoasymmetric, and four *meso* forms result. The remainder of the isomers (9-16) constitute four racemic modifications. The question concerns the properties of these eight forms in each of which the only difference between the A - B - on one end and the $-B$ - A on the opposite end of the molecule is in the sign of one of the A 's or B 's. Thus, in the molecule 9, the two B 's are both *dextro*, but one A is *dextro* and the other *levo*. Is C truly asymmetric in this molecule; i.e., does it affect plane-polarized light and contribute to the rotation of the molecule as a whole? There are two possible solutions, neither of which has as yet been established by experiment.

| | | | | | | | | | | | | | | | | |
|-----|------|---|------|---|-------------------|-----------|----------|-----------|------|----|------|----|------|----|------|----|
| A | + | - | + | - | + | + | + | + | + | - | + | - | + | - | + | - |
| B | + | - | - | + | + | + | - | - | + | - | + | - | + | - | + | - |
| C | | | | | \oplus | \ominus | \oplus | \ominus | - | + | + | - | + | - | - | + |
| B | + | - | - | + | - | - | + | + | + | - | + | - | - | + | - | + |
| A | + | - | + | - | - | - | - | - | - | + | - | + | + | - | + | - |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 |
| | dl | | dl | | <i>meso</i> forms | | | | dl | | dl | | dl | | dl | |

FIG. 49

According to the first possibility C may be truly asymmetric, since there is no plane of symmetry, in which case the forms 9-16 will constitute four racemic modifications. Each form will have rotations and physical properties different from those of all the others except its own mirror image.

On the other hand, the slight differences represented by $\begin{smallmatrix} A+ \\ B+ \end{smallmatrix}$ and $\begin{smallmatrix} B+ \\ A- \end{smallmatrix}$ as in form 9 may not enable C to contribute to the total rotation of the molecule. If this happened in the molecule under consideration then forms 9 and 11 would have the same optical rotation but would differ in other physical properties. The same would be true of the pairs, 10 and 12, 13 and 15, 14 and 16.

Compounds Containing Asymmetric Carbon Atoms in a Branched-Chain Structure

The preceding discussion has been limited to a consideration of the optical isomers of compounds in which the asymmetric carbon atoms were present in a single carbon chain. In branched-chain compounds the number of isomers varies somewhat. As long as all the asymmetric carbon atoms are different the total number of isomers is equal to 2^n .

Thus, in a molecule of the type in Fig. 50, in which A^* , B^* , and D^* are different groups containing an asymmetric carbon atom, the central atom C is also asymmetric; hence, since there is a total of 4 asymmetric carbon atoms there will be 2^4 or 16 isomers existing as 8 racemic modifications. In a molecule of the structure shown in Fig. 51, there are

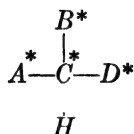


FIG. 50

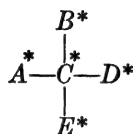


FIG. 51

5 different asymmetric carbon atoms, and hence 2^5 or 32 optical isomers (16 racemic modifications). In these types of branched-chain compounds, therefore, the number of isomers is the same as exists for a chain compound with the same number of different asymmetric carbon atoms.

Special Cases

Molecules containing three similar asymmetric carbon atoms attached to a single carbon atom exist in only four active forms constituting two racemic modifications. These forms are represented in Fig. 52, in which the capital letter A represents an asymmetric carbon atom and three such groups are attached to a central carbon shown by the tetrahedron. It is evident that the central carbon is never asymmetric under

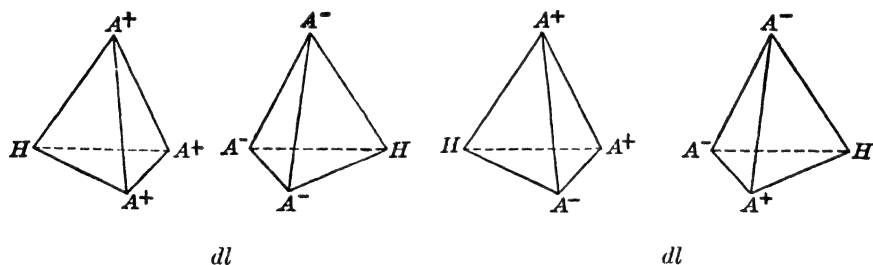


FIG. 52

these conditions, since either two or three groups attached to it are identical. In constructing models of these compounds, and also in representing their arrangement on paper, it is important to note that the mirror image of A^+ is A^- .

A compound with four similar asymmetric carbon atoms (A) attached to a single carbon may exist in two racemic and a *meso* modification, as indicated by the formulas of Fig. 53.

If there are two similar asymmetric carbon atoms A, A and one asymmetric group, B , different from A , then there will exist eight active

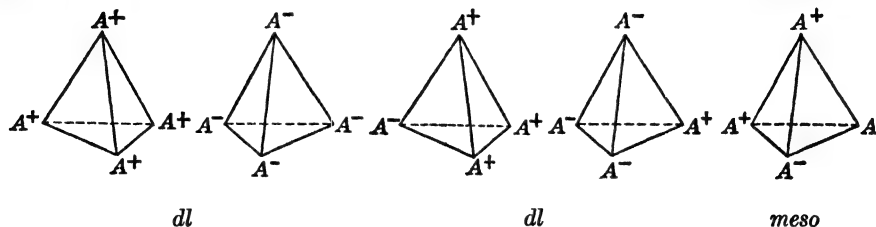


FIG. 53

isomers as four racemic modifications: these are summarized in Figs. 54–61.

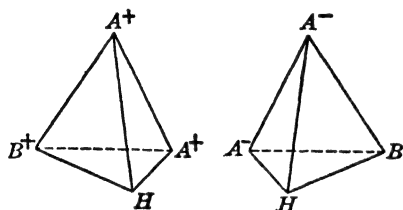


FIG. 54

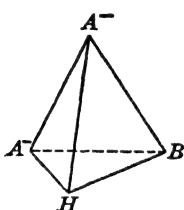


FIG. 55

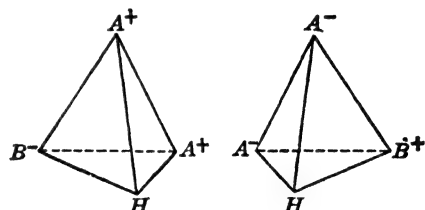


FIG. 56

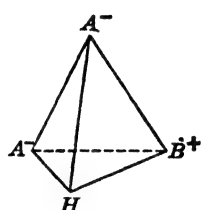


FIG. 57

*dl**dl*

In the first four forms, Figs. 54, 55, 56, 57, the central carbon atom represented by the tetrahedron is not asymmetric, since at least two groups are identical. In the last four forms the central carbon atom has attached to it a $+A$ and a $-A$ in each case. These four models, Figs. 58, 59, 60, and 61, however, are active owing to the group B . No data are available concerning the relative optical and physical properties of isomers like Figs. 58 and 60. The same is true for Figs. 59 and 61. The enantiomorphic forms, Figs. 58 and 59, will have equal rotations opposite in sign and other physical properties identical.

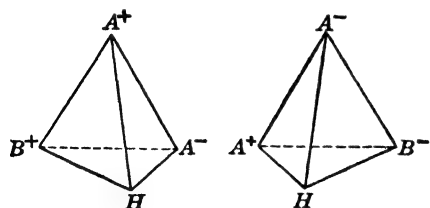


FIG. 58

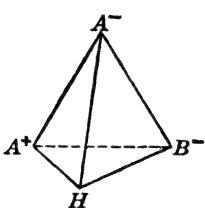


FIG. 59

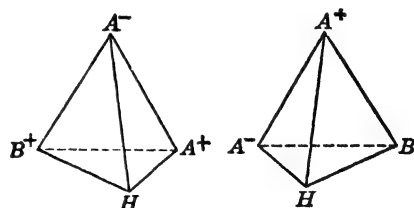


FIG. 60

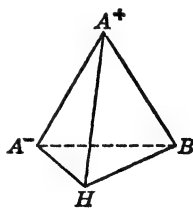


FIG. 61

*dl**dl*

Mathematical formulas have been developed by Senior¹ for calculating the number of isomers in these special cases.

¹ Senior, *Ber.*, **60B**, 73 (1927).

An unusual special case occurs in the oxime (Fig. 63) of a ketone of the type shown in Fig. 62. The ketone has two similar asymmetric car-

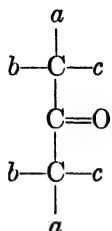


FIG. 62

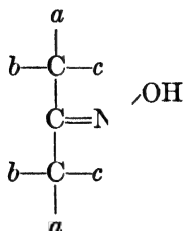


FIG. 63

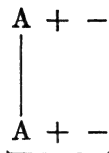


FIG. 64

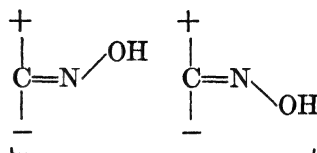


FIG. 65

bon atoms, and hence exists in a racemic and a *meso* modification. The *syn*- and *anti*-oximes of the racemic form of the ketone (Fig. 64) are mirror images of each other, as is evident from the fact that the end groups are identical. The two oximes shown in Fig. 65 are derived from the *meso* form of the ketone and are optically active because they contain no plane of symmetry. The two forms of Fig. 65 are mirror images of each other and constitute a racemic modification. This is rather difficult to visualize from the two-dimensional figures, and it is necessary to construct the models in order to demonstrate the mirror-image relationship.

There are other special cases involving various arrangements of asymmetric carbon atoms, but the number and nature of the isomers can be readily worked out, using the principles discussed above.

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PART IV. RACEMIC MODIFICATIONS

1. Formation

By Synthesis. In the foregoing section it has been pointed out that the conversion of a molecule of the type Ca_2bc into one of the type $Cabcd$ yields a product which is an equimolecular mixture of the *d*- and

l-antipodes called a *racemic* modification. Similarly the synthesis of molecules containing two, three, or more asymmetric carbon atoms results in the formation of racemic modifications. All ordinary chemical reactions carried out on optically inactive compounds without the use of any optically active reagent and in the absence of circularly polarized light invariably produce racemates as the products.

By Mixture of Enantiomorphs. If equimolecular quantities of the *d*- and *l*-antipodes are mixed the resulting product is optically inactive by external compensation and therefore constitutes a racemic modification.

By the Racemization of an Optically Active Form. Optical isomers exhibit varying degrees of stability, and by suitable treatment most of them are ultimately converted to the racemic modifications. If the starting material is the *dextro* form this change involves the conversion of half of this *d*-form to the *l*-form, and vice versa for the racemization of an initial *l*-form. This phenomenon of racemization may be accomplished by purely physical agents such as heat, light, or solution in a solvent. It may also be accomplished by a change in structure involving the formation of an optically inactive intermediate which reverts to the racemic form of the original.

Racemization by Physical Means. Many compounds are racemized by heat. If *d*-tartaric acid is heated with a small amount of water the racemic acid results together with a small amount of the *meso* form. *d*-Phenylbromoacetic acid in benzene solution racemizes in three years on standing at room temperature.¹ Other compounds racemize in a few minutes. Some compounds even racemize while in the solid state, although the change under these conditions is very slow. When racemization occurs spontaneously at room temperature it is called autoracemization.

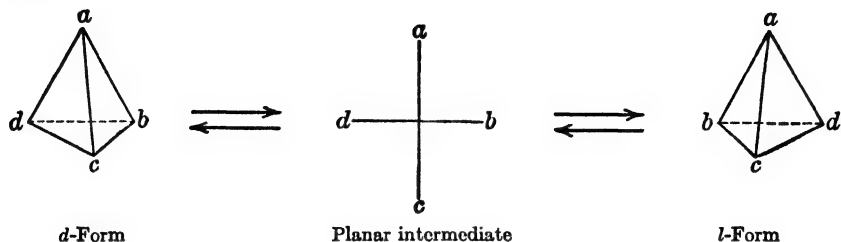
In general it appears that compounds which have reactive functional groups directly attached to the asymmetric carbon atom undergo racemization more easily than similar molecules in which the functional groups are remote from the asymmetric carbon atom.

The mechanism of racemization taking place under the influence of physical agents has been ascribed by Werner² to vibrations of the groups. If the groups acquire sufficient energy so that the amplitude of the vibrations is great enough to bring the four groups momentarily into a plane then it is evident that either the *d*- or *l*-forms may result. Werner² illustrated the racemization of a compound containing an asymmetric carbon atom by a spherical model. Using the present-

¹ Walden, *Ber.*, **31**, 1416 (1898).

² Werner, "Lehrbuch der Stereochemie," Jena (1904), p. 49.

day tetrahedral concept the racemization would be represented as follows:



There is, of course, no proof of such a mechanism. The energy content of optical enantiomorphs is identical, but this does not mean that the interconversion is easy. A considerable amount of activation energy may be necessary to effect the interconversion. A curve representing the change in activation energy with composition is shown in Fig. 1.

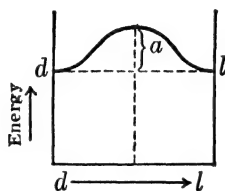


FIG. 1

If the energy difference (a in Fig. 1) between the d - or l - and the optically inactive planar intermediate is great then the interconversion is difficult and requires drastic conditions, whereas if the difference is small then autoracemization takes place.

Computation of the energy required to form the planar intermediate (shown above) shows that this mechanism is rather improbable. The activation energy for this process appears to be about 88 kcal. per mole.³ Since only about 58.6 kcal. is required to break a carbon-carbon bond it appears that purely thermal racemizations probably occur through some process which involves breaking of a bond attached to the asymmetric carbon atom rather than vibration of the groups into a planar arrangement.

It has been found that *l*-butanol-2 undergoes partial racemization when its vapors are passed over zinc chromite, copper, or chromium oxide at temperatures from 132° to 218° whereas no racemization occurred over Pyrex glass at 600°. Calculations show that the racemization is probably not due to reverse reactions from either dehydrogenation or dehydration but very likely is due to a dissociative adsorption of

³ Kincaid and Henriques, *J. Am. Chem. Soc.*, **62**, 1474 (1940).

the alcohol by the catalyst.⁴ Such a process involves actual breaking of one of the bonds directly attached to the asymmetric carbon atom.

The kinetics of racemization has been studied by many investigators⁵ and the determination of the velocity constants and the half-life periods of optical isomers has proved to be of great value, particularly in correlating ease of racemization with certain structural factors such as the size of the groups in the biphenyls.

Racemization is a *reversible* monomolecular reaction. The equations for the calculations of the velocity constants may be derived as follows:

Consider the racemization of a pure *d*-form,



If a = initial concentration of the *d* and x the amount of *d* changing to *l* in the time t , and k_1 and k_2 the velocity constants, then, since $k_1 = k_2 = k$ because the rate of change of the *d*-form is equal to the rate of change of the *l*-form, the differential equation becomes

$$\frac{dx}{dt} = k(a - x) - kx = k(a - 2x)$$

Integrating,

$$k = \frac{2.3}{2t} \log_{10} \frac{a}{a - 2x}$$

Since the concentrations are proportional to the rotations, if α_0 is the original rotation and α_t the rotation at the end of the time t , i.e.,

$$\alpha_0 \propto a$$

$$\alpha_t \propto (a - 2x)$$

then

$$k = \frac{2.3}{2t} \log_{10} \frac{\alpha_0}{\alpha_t}$$

The half-life period T represents the time in which one-fourth of the original *d* has been converted to *l* and is calculated from the equation:

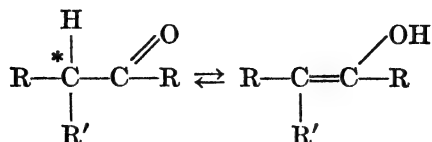
$$T = \frac{2.3}{2k} \log_{10} 2$$

Racemization Involving Tautomerization. If the asymmetric carbon atom is in the α -position to a group capable of undergoing tautomeric

⁴ Burwell, *ibid.*, **59**, 1609 (1937).

⁵ Smith, *ibid.*, **49**, 43 (1927); Campbell and Campbell, *ibid.*, **54**, 3834, 4581 (1932).

change⁶ then racemization takes place very readily. The enolization of a ketone may be represented by the following general equation.



Enolization destroys the asymmetry of the molecule, and hence when the enol form reverts to the keto form the probability of obtaining the *d*-form is equal to the probability of obtaining the *l*-form thus resulting in the racemic modification. In support of this mechanism, it has been found that, whereas mandelic acid (Fig. 2) readily undergoes racemization,

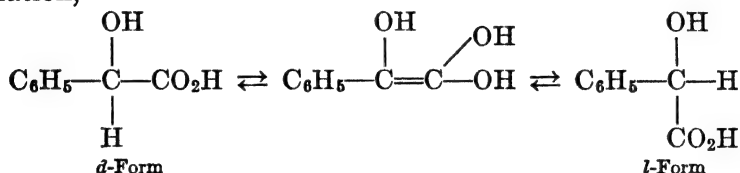
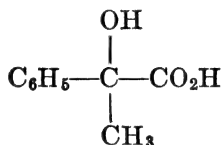


FIG. 2

the active atrolactic acids (Fig. 3) are stable and do not undergo racemization;⁷ the stability is due to the fact that no hydrogen atom is present on the asymmetric carbon atom and hence enolization is not possible.



Atrolactic acid

FIG. 3

McKenzie and Smith⁸ studied the ease of racemization of the following series of amides and found that *l*-atrolactamide (Fig. 4) does not

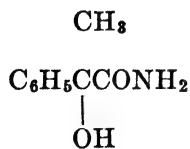


FIG. 4

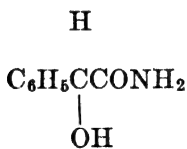


FIG. 5

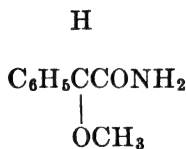


FIG. 6

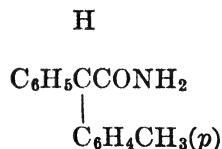
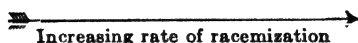


FIG. 7



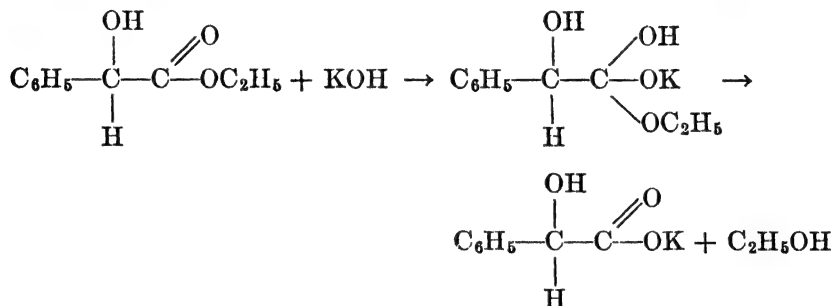
⁶ Kipping and Hunter, *J. Chem. Soc.*, **83**, 1009 (1903).

⁷ McKenzie and others, *ibid.*, **107**, 702, 1681 (1915); **123**, 1962 (1923); *Ber.*, **58**, 894 (1925); Schulze and Bosshard, *Ber.*, **18**, 388 (1885); Rothe, *Ber.*, **47**, 843 (1914); Wren, *J. Chem. Soc.*, **113**, 210 (1918).

⁸ McKenzie and Smith, *J. Chem. Soc.*, **121**, 1348 (1922).

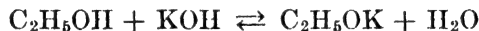
undergo racemization in the presence of traces of alkali or potassium ethoxide in absolute alcohol. The other amides (Figs. 5, 6, and 7) show increasing rates of racemization, which phenomenon parallels the ease of enolization of these compounds.

McKenzie and Wren⁹ have studied the action of alkaline reagents on active esters. Saponification of *l*-ethyl mandelate with dilute aqueous alkalis causes little or no racemization, but the action of alcoholic potassium hydroxide causes considerable racemization. The explanation is based on the fact that aqueous alkalis cause saponification by the following reaction:

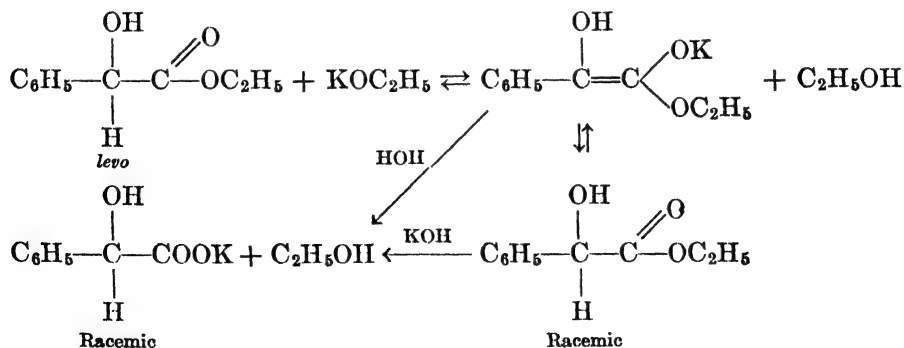


The asymmetric carbon atom is not affected and hence the product retains its activity.

However, when alcoholic potassium hydroxide is the reagent the solution contains some potassium ethoxide.



The potassium ethoxide reacts with the optically active ester to produce the ester enolate which is optically inactive and is in equilibrium with the racemic ester. Hydrolysis of either the optically



inactive ester enolate or the racemic ethyl mandelate would, of course, produce racemic potassium mandelate.

⁹ McKenzie and Wren, *ibid.*, **115**, 602 (1919); Erlenmeyer, Schenkel, and Epprecht, *Helv. Chim. Acta*, **20**, 367 (1937).

Conant and Carlson¹⁰ studied the rates of enolization of five optically active ketones of the type shown in Fig. 8 by noting the rates of racemi-

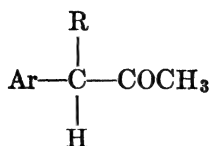
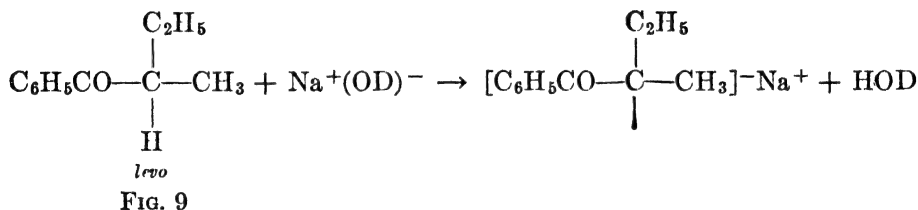


FIG. 8

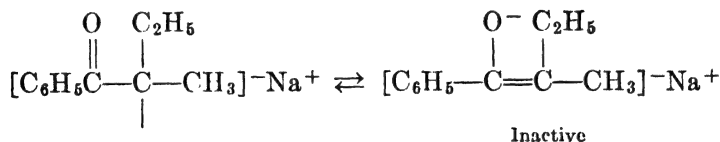
zation. The relative rates were found to be dependent on the nature of the catalyst and solvent.

The use of deuterium compounds has been introduced in order to obtain experimental evidence on the interrelationship between enolization and racemization. Hsü, Ingold, and Wilson¹¹ compared the rate of racemization of the optically active *l*-phenyl *sec*-butyl ketone (Fig. 9) with the rate of introduction of deuterium when the ketone was treated with sodium deuterioxide in dioxane-deuterium oxide solution. The steps in the process are probably:

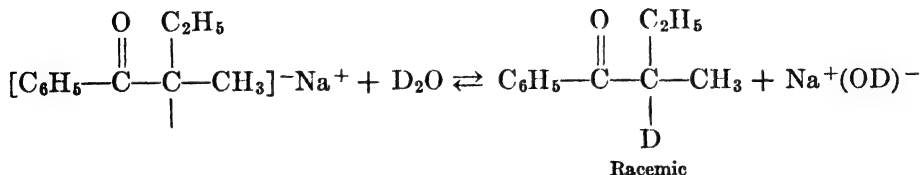
1. Formation of anion.



2. Racemization.



3. Regeneration of ketone.



¹⁰ Conant and Carlson, *J. Am. Chem. Soc.*, **54**, 4048 (1932).

¹¹ Hsü, Ingold, and Wilson, *J. Chem. Soc.*, 78 (1938). See also Ingold and Wilson, *J. Chem. Soc.*, 773 (1934); Bartlett and Stauffer, *J. Am. Chem. Soc.*, **57**, 2580 (1935); Hsü and Wilson, *J. Chem. Soc.*, 623 (1936).

By means of a large excess of deuterium oxide the third reaction can be driven to completion for all practical purposes. It was actually found that the rate of racemization of the optically active ketone paralleled the rate of introduction of deuterium. Both processes followed the first-order rate law within experimental error. The actual rates were not quite identical, but this is ascribed to the fact that the deuterium oxide contained some protium oxide. Protium exchanges at a more rapid rate than deuterium, and hence the ketone racemized a little more rapidly than would have been anticipated if deuterium alone had been introduced.

If a monobasic acid derived from a sugar is dissolved in pyridine or quinoline and heated, a change in the configuration of the asymmetric carbon atom *alpha* to the carboxyl group takes place. Figures 10, 11, 12,

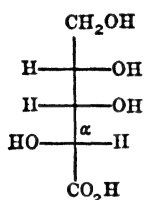


FIG. 10

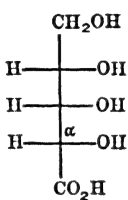


FIG. 11

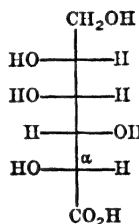


FIG. 12

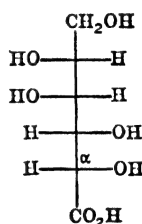


FIG. 13

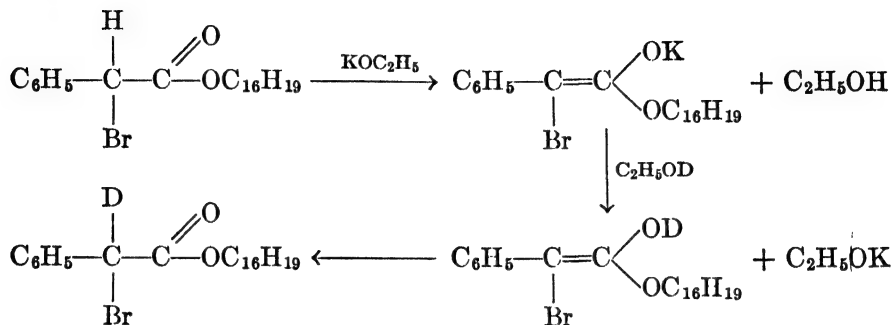
and 13 represent the interconversion of *l*-arabonic and *l*-ribonic and of *d*-gluconic and *d*-mannonic acids. The basic solvent used prevents lactone formation and also catalyzes the transformation to an enolic intermediate which obviously can affect only the configuration of the α -carbon atom. The reaction is reversible and hence represents a configurational change of the α -asymmetric carbon atom whereas the other asymmetric carbon atoms are unaffected. Such a change in the configuration of one asymmetric carbon atom in a molecule which contains two or more asymmetric carbon atoms is called *epimerization*. This epimerization of the sugar acids discovered by Emil Fischer¹² is not a true racemization since the products are diastereoisomers and not mirror images. The formation of these epimers is best explained on the assumption of an enolic intermediate.

Evidence supporting this concept has been obtained by Erlenmeyer¹³ and his associates, who found that treatment of *l*-menthyl *d*-phenylbromoacetate in ethyl deuterioxide with potassium ethoxide caused epimerization to take place rapidly. An isotopic analysis of the recov-

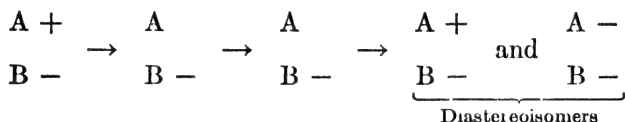
¹² Fischer, *Ber.*, **23**, 799 (1890); **24**, 2137, 3622, 4215 (1891); **27**, 3193 (1894).

¹³ Erlenmeyer and co-workers, *Helv. Chim. Acta*, **19**, 129, 543, 1053 (1936); *ibid.*, **20**, 367 (1937).

ered ester showed that 0.702 hydrogen atom had been replaced by deuterium per mole. The theoretical exchange value is 0.70 calculated from consideration of the equilibria and assumption of enolization be-



fore epimerization. It should be noted that the above process involves the following stereochemical changes:



2. Properties of Racemic Modifications

The physical properties of a racemic modification generally differ from those of the enantiomorphs from which it is derived. The relationships between some of the physical constants of the racemic and the optically active forms are discussed below.

A racemic modification may exist in three forms in the solid state. These solid phases may be racemic mixtures, racemic compounds, or racemic solid solutions. Analogous types are found among many common inorganic salts. Thus, copper calcium acetate exists as a mixture of the two salts above 75° but forms the double salt below this temperature. The racemic solid solution is analogous to isomorphous crystals, such as the alums which form mixed crystals in all proportions.

Racemic Mixture. This modification is a mechanical mixture of individual crystals of the *dextro* and *levo* forms. In some compounds, notably in sodium ammonium tartrate, the crystals may possess hemihedral facets and be themselves enantiomorphous (Figs. 14 and 15). When carefully formed, they may be distinguished from each other with the aid of a hand lens and separated mechanically.

Racemic Compound. A pair of enantiomorphs can often unite to form a molecular compound, all the crystals of which contain equal

amounts of both isomers and are identical. Heat is usually evolved during its formation, and its physical properties are markedly different from those of its components. Since, however, almost complete dissociation occurs when compounds of this type dissolve, ordinary cryoscopic methods fail to establish a multiple molecular weight.¹⁴ Presence of an excess of one of the active modifications, however, limits the extent of the dissociation. Thus Walden¹⁵ and Patterson¹⁶ have been able to show that the values for the molecular weight of racemic diacetyl tartrate are considerably greater when determined in active diacetyl tartrate as the solvent than in water as the solvent.

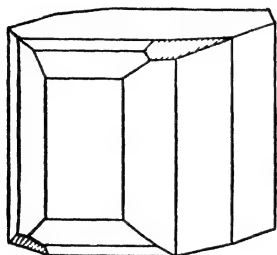


FIG. 14*

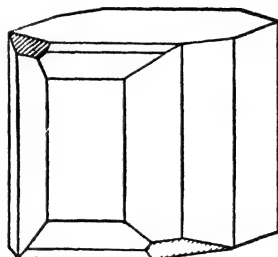


FIG. 15*

Racemic Solid Solution.† If a pair of enantiomorphs are also isomorphous, they may crystallize together as a solid solution without formation of a compound. This modification differs from a racemic mixture in that it constitutes but a single phase, as does a racemic compound. However, it differs from the latter in that all mixtures composed of a racemic solid solution and either active form still act as a single phase, whereas any mixture composed of a racemic compound and either active form constitutes two phases.

Methods for Determining the Nature of Racemic Modifications.

In order to distinguish between these three types of racemic modifications, Roozeboom¹⁷ has devised two methods.

Freezing-Point Method. This method requires the preparation of a freezing point-composition diagram for mixtures of the racemic modifica-

* Cohen, "Theoretical Organic Chemistry," The Macmillan Co., New York (1928). (Courtesy of the publishers.)

¹⁴ Raoult, *Z. physik. Chem.*, **1**, 186 (1887); Anschütz, *Ann.*, **247**, 121 (1888); Frankland and Pickard, *J. Chem. Soc.*, **69**, 128 (1896); Bruni and Padoa, *Gazz. chim. ital.*, **32**, 503 (1902).

¹⁵ Walden, *Ber.*, **39**, 666 (1906).

¹⁶ Patterson, *Ber.*, **38**, 4092 (1905).

† The term "pseudoracemic mixed-crystal," hitherto used to describe this modification, was introduced by Kipping and Pope.

¹⁷ Roozeboom, *Z. Physik. Chem.*, **28**, 494 (1899).

tion with its corresponding antipodes. One may then distinguish between the three types in that the diagram for a racemic mixture is composed of two curves (Fig. 16); for a racemic compound, of three curves (Figs. 17 or 18, depending upon whether the freezing point of the racemic compound is higher or lower than that of the antipodes); and for a racemic solid solution, one line (Fig. 19).

Since each of the possible diagrams is symmetrical, only one of the enantiomorphs, together with the racemic modification, is necessary for the study.

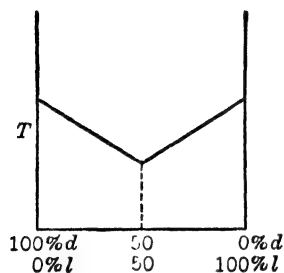


FIG. 16

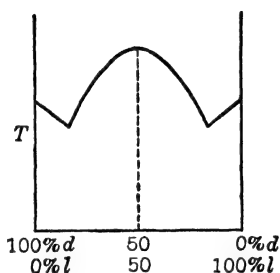


FIG. 17

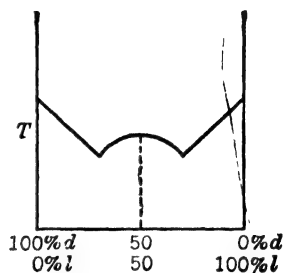


FIG. 18

In order to determine whether a racemic mixture or racemic compound is formed, it is merely necessary to add a small amount of either the pure *d*- or pure *l*-form to the racemic modification and determine the freezing point. If this freezing point is higher than that of the original racemic modification a racemic mixture is present; if lower, a racemic compound is indicated. As is evident from the diagrams of Figs. 17 and 18, care must be taken not to add too much of the *d*- or *l*-form since the freezing point of this composition might fall close to one of the vertical axes and a rise in freezing point would be obtained.

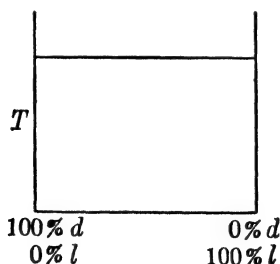


FIG. 19

This method cannot be used if the components form a racemic solid solution since the liquidus and solidus curves become identical and hence there is only a straight horizontal line between the identical melting points of the *d*- and *l*-forms. (See Fig. 19.)

Solubility Method. Roozeboom¹⁷ and also Bruni¹⁸ have discussed the solubility relationships which should exist between optical enantiomorphs, racemic mixtures, racemic compounds, and racemic solid solutions from considerations of the phase rule. The curves shown have not been established experimentally, nor have their exact shape and slope been determined. No experimental data have been presented which definitely correlate the melting-point curves given above with solubility curves.

According to Roozeboom, just as the presence of a second fusible solid phase lowers the melting point of an organic compound, so the presence of a second soluble phase alters its solubility. Hence, if a solubility-composition isotherm for mixtures of a racemic modification with its corresponding enantiomorphs is plotted, the result is the same as in the previous method, i.e., a racemic mixture gives rise to two curves, a racemic compound to three curves, and a racemic solid solution to one curve. Here, again, the diagrams are symmetrical, so that only one of the active isomers is needed for the study.

The conclusions drawn from this method are valid only for the particular temperature at which the solubilities are determined. Suppose, for example, that a substance crystallizes from water as a racemic mixture at a temperature t_1 . The solubility-composition isotherm, t_1 (Fig. 20), then has the form acb , where a and b are the solubilities of the pure d -form and pure l -form, and c the solubility of the mixture.* The

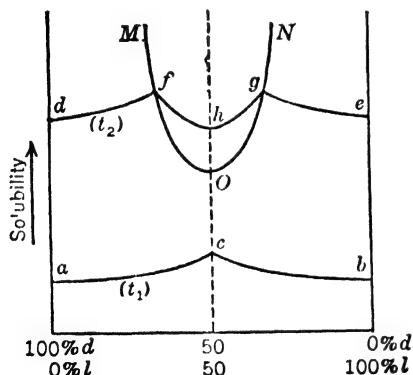


FIG. 20

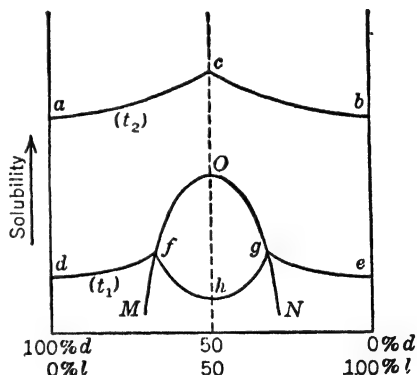


FIG. 21

branches ac and bc then represent the change in solubility of each form as the other form is added. It often happens, however, that the same racemic modification can crystallize as a compound at a higher temper-

¹⁸ Bruni, *Gazz. chim. ital.*, **30**, 35 (1900).

* The shape of these curves depends on the nature of solute and solvent. The point c may also lie on a straight line between a and b or may be below the value for a or b .

ature, t_2 . Its solubility-composition isotherm then has the form $dfhge$; df and eg have the same meaning as ac and bc , but instead of being joined together directly, they are attached to the curve fhg , in which h represents the solubility of the racemic compound, and hf and hg represent the change in its solubility in the presence of increasing amounts of the d - and l -forms, respectively. The points f and g therefore represent solutions saturated with respect in the one case to racemic compound and d -form, in the other to racemic compound and l -form. If solubility-composition isotherms for temperatures lower than t_2 are plotted, the points f and g approach each other along the curves MO and NO , respectively, until they meet at O . The temperature at which this occurs is the transition temperature for the racemic modification concerned. Above that temperature it will crystallize only as a racemic compound; below it, as a racemic mixture. An example is sodium ammonium tartrate with a transition temperature of 27.7° .

For some racemic modifications the situation is reversed. In this event the curves appear as in Fig. 21, where the racemic mixture is now the form stable above the transition temperature, and the racemic compound is the form stable below. An example is rubidium tartrate with a transition temperature of 40.4° .

The solvent, especially when the solute can crystallize with solvent of crystallization, plays an important role in determining which form the racemic modification possesses in the solid state. Thus sodium ammonium tartrate as a racemic mixture crystallizes with four moles of water for each form, but as a racemic compound with only two; and rubidium tartrate crystallizes as a racemic compound with two moles of water of crystallization but as a racemic mixture with none. In general, the form possessing the smaller number of moles of water of crystallization is the form obtained above the transition temperature.

Racemic modifications sometimes crystallize from one solvent as a mixture, from another as a compound. Here, too, solvent of crystallization probably plays an important role.

Transition temperatures at which a racemic compound becomes a racemic solid solution have also been observed. Thus racemic camphoroxime, above 103° , crystallizes as a solid solution. When this cools to 103° or below, the solid solution becomes a compound; the reverse change takes place upon reheating to 103° .

The foregoing discussion outlines the solubility relationships of the active forms and the racemic mixtures and compounds. In order to distinguish between a racemic mixture and a racemic compound it is only necessary to add a crystal of the pure d - or l -form to a saturated solution of the racemic modification at the proper temperature. In the case of

the racemic mixture, the crystal does not dissolve, since the solid phase of a racemic mixture contains crystals of the *d*- and *l*-forms. Hence, the solution remains optically inactive. However, the addition of crystals of either isomer to a saturated solution of a racemic compound results in the presence of a new solid phase. The crystal dissolves and the supernatant liquid becomes optically active.

If this solubility test is applied to a saturated solution of a racemic solid solution the same results are obtained as if a racemic mixture were used. This method, therefore, does not distinguish between racemic mixtures and racemic solid solutions.

In addition to the two methods just described Bruni¹⁹ developed a third procedure which involves a study of the eutectics of mixtures of the two active forms with a third inert substance. This method can be illustrated by Adriani's²⁰ study of camphoroxime. The melting-point curve of mixtures of the pure *d*-oxime with naphthalene was first studied in order to determine the composition of the eutectic. Various mixtures of *d*- and *l*-camphoroxime were then made up and added to naphthalene in the same proportion as in the eutectic mixture of the pure *d*-form and naphthalene. The freezing-point curves of these mixtures were determined and a plot of the data obtained is shown in Fig. 22. Figures 23, 24, and 25 show the data obtained when phenan-

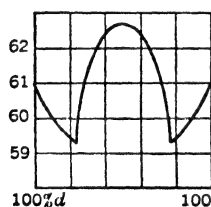


FIG. 22

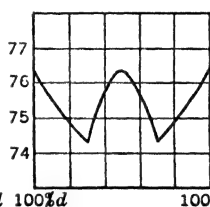


FIG. 23

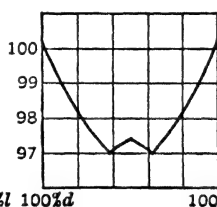


FIG. 24

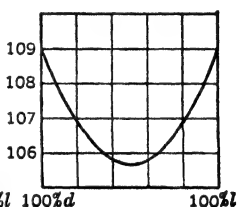


FIG. 25

threne, benzoin, and anthracene were used in place of naphthalene. The curves indicate that between 60 and 90° *dl*-camphoroxime exists as a racemic compound, but at 106° as a racemic solid solution.

Existence of a Racemic Compound in the Liquid State. While many experiments have been performed in attempts to establish the existence of liquid racemic compounds, the only satisfactory evidence is that obtained from diagrams such as those of Figs. 17 and 18. The flatness of the freezing-point curve at its maximum is an approximate measure of the degree of dissociation of the racemic compound *at its freezing point*. By means of this fact, Ross and Somerville²¹ showed that racemic cam-

¹⁹ Bruni, *Atti. accad. Lincei*, [5] **8** 1, 332 (1899); *Gazz. chim. ital.*, **30**, 35 (1900).

²⁰ Adriani, *Z. physik. Chem.*, **36**, 168 (1901).

²¹ Ross and Somerville, *J. Chem. Soc.*, 2770 (1926).

phoric acid dissociated upon melting to the extent of about 12 per cent, and, similarly, racemic methyl hydrogen camphorate about 18 per cent. On the other hand, for temperatures above their freezing point, liquid racemic substances always behave as mixtures.

3. Resolution of Racemic Modifications

The fact that optical antipodes have the same physical properties, with the exception of the effect on polarized light, means that special methods must be used in order to separate them. It was Pasteur who accomplished the first separation of the optical forms from a racemic modification and developed many of the procedures for resolution.

(a) **Mechanical Separation of Crystals.** When a racemic modification is allowed to crystallize from a solution under conditions which permit the separation of a racemic mixture then the solid phase consists of two kinds of crystals, one of which is composed of the *dextro* and the other of the *levo* isomer. If these crystals possess hemihedral facets which permit them to be distinguished from each other, then they may be separated by means of a pair of tweezers and a hand lens. It was in this manner that Pasteur²² in 1848 separated the *d*- and *l*-forms of sodium ammonium tartrate, the crystal forms of which are shown in Figs. 14 and 15 (p. 249).

This method has found useful application in only a few instances. It cannot be used to resolve racemic compounds or solid solutions which do not possess convenient transition temperatures permitting crystallization as racemic mixtures. Also, many racemic crystals do not possess the requisite hemihedrism by which they may be distinguished. Even where definite hemihedral crystals are possible, considerable skill and patience are required to grow suitable crystals.

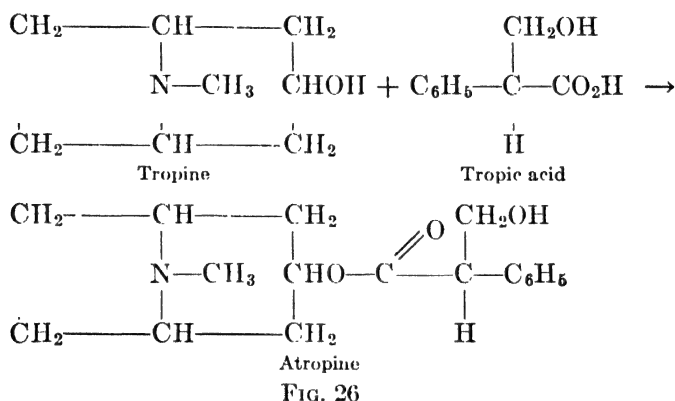
(b) **Preferential Crystallization Due to Inoculation.** A more practical way of accomplishing a direct separation of the enantiomorphs in a racemic mixture is in some way to cause but one of the forms to crystallize from a supersaturated solution of the mixture, leaving the other behind.

It has been found that an aqueous solution of racemic ammonium hydrogen malate deposits an initial crop of crystals which are optically active and which are found to consist of three parts of the *l*-salt to one part of the *d*-salt. Thus a partial resolution of the *dl*-malate has taken place. Malic acid has been resolved by crystallization of inactive ammonium molybdomalate. The preferential separation of one form depends on inoculation of a supersaturated solution with an active form.

²² Pasteur, *Ann. chim. phys.*, [3] **24**, 442 (1848).

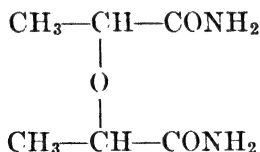
Lactic acid has been resolved by inoculation of a concentrated solution of the zinc ammonium salt with crystals of the active salt. In some instances, merely an isomorphous substance may be used as the inoculum. A crystal of *l*-asparagine when added to a solution of *dl*-sodium ammonium tartrate causes pure sodium ammonium *d*-tartrate to crystallize out first. Some experiments have been reported in which the inoculating crystals need not be optically active or even possess an asymmetric atom.

Quite recently Anderson and Hill²³ have observed a spontaneous resolution of atropine sulfate (Fig. 26). Repeated crystallization of this *dl*-salt from absolute alcohol yielded the *d*- and *l*-hyoseyamine sulfate



with $[\alpha]_D = \pm 20^\circ$. The atropine sulfate was prepared by racemization of *l*-hyoseyamine and also by synthesis from synthetic tropic acid and tropine, but the spontaneous resolution occurred with both samples. Anderson and Hill attribute the spontaneous resolution to inoculation from the atmosphere since the results obtained varied depending on whether or not the crystallizations were carried out in laboratories where *l*-hyoseyamine had been used in other experiments.

The *dl*-form of dilactyldiamide,²⁴



is spontaneously resolved by crystallization from water provided the temperature is above 35° . *dl*-Histidine monohydrochloride also has been resolved spontaneously.²⁵

²³ Anderson and Hill, *J. Chem. Soc.*, 993 (1928).

²⁴ Viéles, *Compt. rend.*, **198**, 2102 (1934).

²⁵ Duschinsky, *Chemistry & Industry*, 10 (1934).

It can readily be seen that this method avoids some of the objections to the use of the first method. Moreover, a spontaneous crystallization of one form can occur even if the racemic modification is a compound provided this compound is more soluble than its component enantiomorphs.

(c) **Conversion to Diastereoisomers.** This method was also originated by Pasteur and elaborated by other investigators. It has already been pointed out that diastereoisomers have different physical properties; hence, if a racemic modification is combined with some readily available optically active reagent, two diastereoisomeric forms result which may be separated by fractional crystallization.* After separation, the original active group is split off from each of the diastereoisomers separately and the *d*- and *l*-forms of the original racemate are obtained. As an example, the separation of a racemic acid, represented by *d*lA, may be considered. Combination with an active base (*l*B) gives the two diastereoisomeric salts:



These salts are not enantiomorphous and hence possess different solubilities and may be separated by fractional crystallization from a suitable solvent. After separation, the *d*A·*l*B is treated with mineral acids or alkalis and the *l*B split off leaving the *d*A form. In a similar way the *l*A·*l*B salt yields the *l*A form.

Racemic bases may be resolved by an optically active acid in an analogous manner.

This general method for obtaining both forms possesses some difficulties in actual practice. Some of the causes of failure to obtain resolution of a racemic modification are:

(a) The salts *d*A·*l*B and *l*A·*l*B may separate as oils which cannot be made to crystallize. The only resort then is to try other optically active bases until good crystalline salts are obtained.

(b) The two components may form a "diastereo compound,"† *d*lA·*l*B. If the transition temperature at which this compound is dissociated into the diastereo mixture, *d*A·*l*B + *l*A·*l*B, lies outside the temperature range at which crystallization can occur, and if it is less soluble than either of its component diastereoisomers, then no separation can be effected and the resolution fails.

* It has recently been reported that diastereoisomers may be separated by fractional distillation through a very efficient packed column. See Bailey and Hass, *J. Am. Chem. Soc.*, **63**, 1969 (1941).

† Also known as "partially racemic compound." The term "partially racemic" is self-contradictory.

(c) The two salts, if isomorphous, may form a continuous series of solid solutions, from which they cannot be separated. It sometimes happens that a portion of one salt separates first, after which the remaining material crystallizes as a solid solution of more or less constant composition.*

(d) The two salts may possess such slight differences in solubility that the resolution becomes quite tedious. Under such circumstances a variation in procedure introduced by Pope and Peachey²⁶ is frequently successful. It consists in neutralizing the inactive base dIB with an equimolecular mixture of an active acid, dA , and a mineral acid such as hydrochloric acid. Four salts are formed, $dA \cdot IB$, $dA \cdot dB$, IB hydrochloride, and dB hydrochloride. If the $dA \cdot IB$ is the least soluble salt it crystallizes first. This disturbs the equilibrium among the salts remaining, so that more $dA \cdot IB$ is formed from the $dA \cdot dB$ and IB hydrochloride. This new $dA \cdot IB$ then separates and the process continues until most of the IB has crystallized as $dA \cdot IB$, and the dB remains in solution as the hydrochloride. This modification fails, however, if the two diastereoisomers crystallize as compounds or solid solutions, rather than as mixtures. The hydrochloride of the base must, of course, be very soluble.

(e) When the salt $dA \cdot IB$ is considerably the less soluble, it is obtained pure after but few crystallizations, and the dA regenerated from it is optically pure. However, the more soluble $lA \cdot IB$ remaining in the mother liquor is contaminated with a small amount of $dA \cdot IB$ and is difficult to obtain optically pure. In order to do so, it is sometimes possible to find another solvent in which the $lA \cdot IB$ is the less soluble and then, by its use, the pure salt can be separated. Decomposition of this salt yields pure lA . A second method for obtaining pure lA consists in decomposing the impure salt and combining the resulting impure lA with other active bases until a pair of diastereoisomeric salts is obtained with the reverse solubility relationship: i.e., the $lA \cdot IB$ is less soluble than the $dA \cdot IB$. By crystallization the former then separates in the pure state and the lA is obtained from it in the optically pure condition.

A third method for obtaining the pure isomer from the more soluble salt has been developed by Marckwald;²⁷ it depends on the fact that the salts $dA \cdot IB$ and $lA \cdot dB$, as well as $lA \cdot IB$ and $dA \cdot dB$, are enantiomorphic and possess the same solubility. Hence, if the partially resolved but impure lA , obtained as described above, be recombined with the

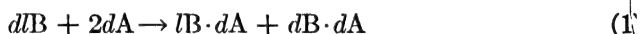
* This behavior is analogous to the formation of azeotropic mixtures of liquids.

²⁶ Pope and Peachey, *J. Chem. Soc.*, **75**, 1066 (1899).

²⁷ Marckwald, *Ber.*, **29**, 43 (1896).

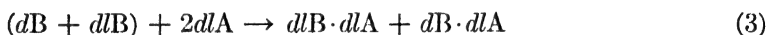
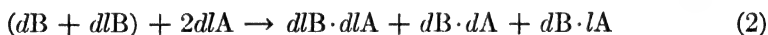
optical antipode of the original active base, the enantiomorphous salt, $lA \cdot dB$, is now less soluble than $dA \cdot dB$ and is the first to crystallize from the solution. In order to accomplish resolution by Marckwald's method it is necessary to have supplies of both the *d*- and *l*-forms of the resolving base in the optically pure state. Since relatively few such pairs are readily available this method has been little used.

The solubility relationships among optically isomeric salts have been investigated by Ingersoll,²⁸ who has devised new methods for the complete resolution of racemic acids and bases. The first step in these procedures is similar to that already described. For example, a racemic base is treated with an active acid and the two salts obtained.



When, for example, the salt $lB \cdot dA$ is the less soluble this salt is recrystallized until pure. Treatment with alkali liberates the pure *l*-base. The mother liquors containing $dB \cdot dA$ and some $lB \cdot dA$ are likewise treated with alkali and the partially resolved base ($dB + dlB$) obtained. New procedures were developed to secure the pure *d*-base from this mixture.

When this mixture is treated with an equivalent amount of the racemic form of the acid originally used (or any other suitable *dl*-acid) the ions in the solution may combine in one of two ways as shown by equations 2 and 3:



In the instances represented by equation 2 the salt $dB \cdot lA$, which is enantiomorphous with the $lB \cdot dA$ of equation 1, may sometimes be the least soluble, and, if so, it crystallizes out first. It is purified by recrystallization, and upon treatment with alkali gives the pure *dB* and also the alkali salt of pure *lA*. Thus both active forms of the base and the acid are obtained.

When equation 3 represents the mode of combination, a complete resolution of the base (but not of the acid) is possible whenever the diastereo compound $dB \cdot dlA$ is less soluble than the racemic salt $dlB \cdot dlA$. Crystallization then yields the $dB \cdot dlA$ salt pure from which alkali liberates the pure *dB* and the alkali salt of the racemic acid.

It is clear, however, that each of these methods depends for its success on a favorable order of the solubility of the isomeric salts involved. When, in equation 1, $lB \cdot dA$ is less soluble than $dB \cdot dA$, then in the salts shown by equation 2 the enantiomorphous salt $dB \cdot lA$ (possessing

²⁸ Ingersoll and co-workers, *J. Am. Chem. Soc.*, **47**, 1168 (1925); **50**, 2264 (1928); **54**, 274, 4712 (1932); **55**, 411 (1933); **56**, 2123 (1934).

the same solubility as $lB \cdot dA$) is less soluble than $dB \cdot dA$; but in addition $dB \cdot lA$ must be less soluble than the racemic salt $dB \cdot dA$. For separation under the conditions represented by equation 3 the diastereo compound $dB \cdot dA$ must be less soluble than the racemic salt $dB \cdot dA$. Many cases corresponding to these solubility relationships have been studied by Ingersoll and his students.

It is evident that the resolution of racemic acids and bases described in the above paragraphs is merely one special example of diastereoisomer formation. Racemic compounds which do not have functional groups capable of salt formation may be converted to diastereoisomeric derivatives by reaction with any suitable optically active reagent. Such a reagent should have the following properties:

1. It should be readily obtainable from easily available starting materials.
2. It should react with the racemic modification in but one way. Thus a dibasic acid, which can form both normal and acid salts, is not so useful a resolving agent as a monobasic acid.
3. It must form compounds with the racemic modification stable enough to resist dissociation or decomposition on recrystallization, yet easily split after separation, by methods not drastic enough to cause racemization.
4. Its diastereoisomeric derivative must be crystallizable and less soluble than any of its components.
5. It should have a high rotatory power in order to enable the progress of a resolution to be followed by polarimetric methods.
6. It should be readily recoverable for repeated use.

The following summary lists the more important compounds which have been used for resolution of racemic modifications.

1. For resolution of racemic acids the following bases have been used.

| | |
|---------------------|--------------------------------|
| Brucine | α -Phenylethylamine |
| Cinchonidine | Phenyl oxynaphthyl methylamine |
| Cinchonine | Quinidine |
| Hydroxyhydrindamine | Quinine |
| Menthylamine | Strychnine |
| Morphine | ψ -Ephedrine |

The benzimidazole bases formed by the condensation of a lactone of a sugar acid with *o*-phenylenediamine have been found useful for resolving certain *dl*-acids. By use of the benzimidazole derived from D-glucose D-guloheptolactone excellent yields of *l*-tartaric acid may be obtained from racemic acid.²⁹

²⁹ Haskins and Hudson, *ibid.*, **61**, 1266 (1939).

2. The following compounds have been used for the resolution of racemic bases.

| | |
|--|---------------------------------|
| α -Bromocamphor- π -sulfonic acid | Menthoxyacetic acid |
| Camphoric acid | Oxymethylene camphor |
| Camphor-10-sulfonic acid | Quinic acid |
| Helicin | Tartaric acid |
| Malic acid | 2,2'-Dinitro-6,6'-diphenic acid |
| Mandelic acid | Diacetyltartaric acid |

3. Racemic alcohols are usually first converted to hydrogen phthalate or hydrogen succinate esters by interaction with phthalic or succinic anhydrides. The acid esters are then resolved in the usual way with an optically active base. From the resolved esters the active alcohols are obtained by saponification. Esters of tartranilic acid have also been used for resolving alcohols.³⁰

l-Menthyl isocyanate and *l*-menthoxyacetyl chloride are also useful resolving agents for alcohols and phenols.

4. Racemic aldehydes and ketones may be resolved by combination with *l*-menthylhydrazine, *d*-isoamylhydrazine, *l*-menthylsemicarbazide, or *d*- α -phenylethylsemicarbazide.

In the case of sugars, *d*-amyl mercaptan has been employed.

5. α -Amino acids are usually resolved through their acyl derivatives. Menthoxyacetyl chloride forms an acyl derivative which consists of a mixture of diastereoisomeric forms.

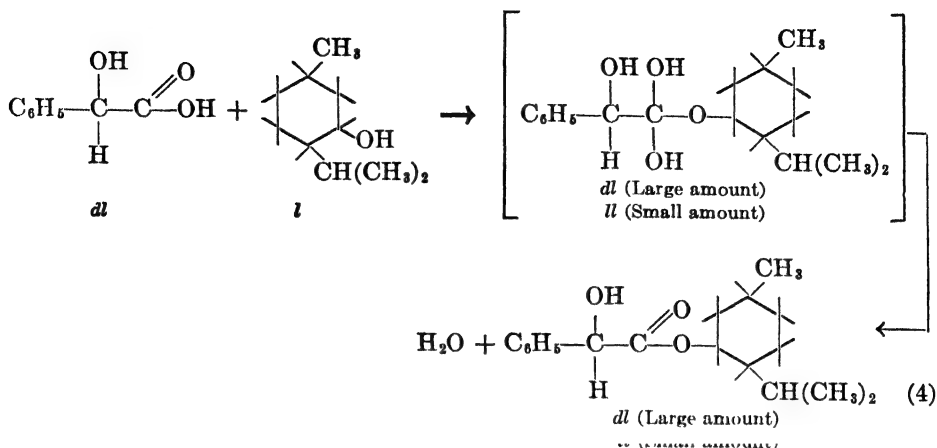
6. Hydrocarbons may be partially resolved by means of their addition compounds with desoxycholic acid.

(d) **Kinetic Method of Resolution.** Marekwald and McKenzie³¹ have shown that *l*-menthol reacts faster with *d*-mandelic acid than with *l*-mandelic acid. Hence, if *dl*-mandelic acid is esterified (equation 4) with a quantity of *l*-menthol insufficient to react with all the acid present the product consists to a large extent of *l*-menthyl *d*-mandelate. If equivalent amounts are used the esterification must be interrupted before the process is complete. The two products of the esterification reaction are diastereoisomers and are produced in unequal amounts under the conditions used. One reason suggested for the inequality in amounts is the fact that esterification probably involves the formation of the intermediate addition compound shown in the brackets. The active *l*-menthol adds to the carbonyl group of the *d*- and *l*-mandelic acids at different rates because of the different steric influences of the

³⁰ Barrow and Atkinson, *J. Chem. Soc.*, 638 (1939).

³¹ Marekwald and McKenzie, *Ber.*, **32**, 2130 (1899); Marekwald and Paul, *Ber.*, **38**, 810 (1905); **39**, 3654 (1906).

groups present. The sensitivity of addition reactions to steric effects of groups has been well established.



Two diastereoisomeric esters composed, for example, of *l*-acid-*l*-alcohol and *d*-acid-*l*-alcohol have also been found to undergo hydrolysis at different rates. Hence if the hydrolysis of a mixture of two such esters is interrupted before it is complete, a predominance of one isomer is found and thus constitutes a partial separation.

Of theoretical interest in connection with heterogeneous catalysis is the observation of Schwab and Rudolph³² that in the catalytic dehydration of *dl*-2-butanol over active quartz the unchanged alcohol was found to be optically active. Apparently the active quartz exhibited a selective adsorption for the *d*- or *l*-forms of the 2-butanol.

Powdered *d*- and *l*-quartz have also been found to exert a selective adsorptive action on the enantiomorphic forms of certain complex cobalt compounds.³³ The resolutions obtained were not complete but the method may serve as a means of determining the resolvability of compounds. Henderson and Rule³⁴ resolved *dl*-*p*-phenylene-bis-iminocamphor by allowing a petroleum ether-benzene solution to flow down a Tswett column packed with lactose. Partial resolution occurred during each passage, and the process had to be repeated many times in order to effect resolution.

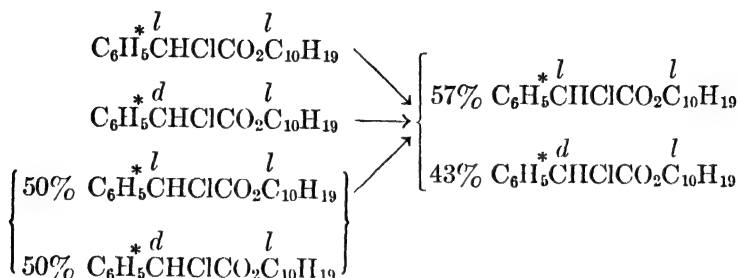
(e) **Equilibrium Method of Resolution.** If the *d*- and *l*-forms constituting a racemic form are readily interconvertible (i.e., racemize easily), then reaction of such a *dl*-form with an active compound may result in unequal amounts of the diastereoisomers even though the reac-

³² Schwab and Rudolph, *Naturwissenschaften*, **20**, 363 (1932).

³³ Tsuchida, Kobayashi, and Nakamura, *J. Chem. Soc. Japan*, **56**, 1339 (1935); *Bull. Chem. Soc. Japan*, **11**, 38 (1936); Karagunis and Coumoulos, *Nature*, **142**, 162 (1938).

³⁴ Henderson and Rule, *Nature*, **141**, 917 (1938); *J. Chem. Soc.*, 1568 (1939).

tion is allowed to run to completion. That is, the equilibrium concentrations of the diastereoisomers are different.³⁵ For example, McKenzie³⁶ prepared the *l*-menthyl esters of *d*-, *l*-, and *dl*- α -chlorophenylacetic acids. Treatment of each of these esters with a trace of alkali in absolute alcohol solution led to the production of the diastereoisomeric esters in 57 per cent and 43 per cent yields respectively at equilibrium. The following diagram summarizes the changes involved.



It is evident that some interconversion of the *d*- and *l*-configurations about the asymmetric carbon atom marked with the asterisk must have taken place in order to account for the composition of the final equilibrium mixture. Recent studies on such transformations have been made by Jamison and Turner.³⁷

The inequality in amounts of the two diastereoisomers may be so great that only one form can be isolated. The relative solubility of the diastereoisomers is a very important factor and assists in shifting the equilibrium. For example, Leuchs³⁸ in resolving the two compounds (Fig. 27 and Fig. 28) by brucine and strychnine obtained only the *d*-forms

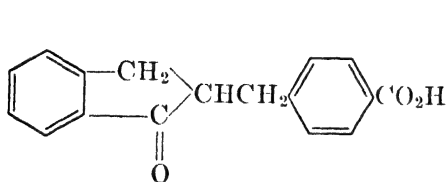


FIG. 27

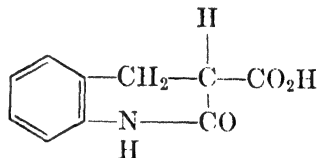


FIG. 28

even though the solution of the salts was evaporated to dryness. Ashley and Shriner³⁹ obtained only the *d*-form of the compound shown in Fig. 29.

³⁵ King, *Ann. Repts. Chem. Soc. (London)*, **30**, 261 (1933).

³⁶ McKenzie and Smith, *Ber.*, **58**, 899 (1925).

³⁷ Jamison and Turner, *J. Chem. Soc.*, 1954 (1937); 1646 (1938); 264 (1940).

³⁸ Leuchs, *Ber.*, **54**, 830 (1921).

³⁹ Ashley and Shriner, *J. Am. Chem. Soc.*, **54**, 4410 (1932).

The biphenyl (Fig. 30), of which merely the *l*-form was obtained, is one of several biphenyl derivatives isolated in only one form by Adams⁴⁰ and his students.

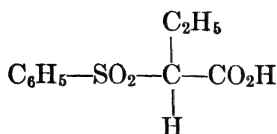


FIG. 29

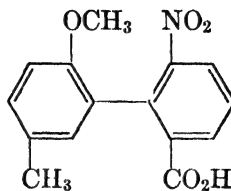


FIG. 30

It is important to note the differences between the two methods of resolution just described. In the kinetic method it is necessary to limit the amount of the active compound used or to stop the reaction at a given time before the reactions are complete. No interconversion of the *d*- and *l*-forms is necessarily involved. In the equilibrium method interconversion of *d*- and *l*-forms takes place, equivalent amounts of reactants may be used, and the reactions are allowed to proceed until equilibrium is established.

(f) **Biochemical Processes.** It has been found that, if a dilute solution of a racemic compound is made to serve as a medium in which bacteria, yeasts, or molds are grown, certain microorganisms tend to destroy one isomer more rapidly than the other. By filtration of the solution through a Chamberland filter and concentration, the unattacked isomer may be obtained. This method was originated by Pasteur⁴¹ who found that the organism *Penicillium glaucum* destroyed *d*-ammonium tartrate more rapidly than the *l*-ammonium tartrate in a dilute solution of *dl*-ammonium tartrate.

It has been found that this same preferential attack upon one of the isomers in a racemic modification occurs in higher organisms. Thus a salt of *dl*-malic acid injected subcutaneously in the rabbit gives rise to *d*-malate in the urine;⁴² similarly, when sodium *dl*-phenyl- γ -oxybutyrate is given to a dog, the urine contains more of the *l*- than of the *d*-isomer.⁴³

The living organism is not necessary to obtain this differential destruction of one form since enzymes will accomplish the same effect. For example, the enzyme emulsin acts on synthetic *dl*-mandelonitrile to destroy the *d*-form more rapidly than the *l*-form. Apparently, since the enzyme itself is optically active, the phenomenon is similar to that involved in method (c) and (d) or in both.

⁴⁰ Chien and Adams, *ibid.*, **56**, 1787 (1934).

⁴¹ Pasteur, *Compt. rend.*, **46**, 615 (1858); **51**, 298 (1860).

⁴² Tomita, *Biochem. Z.*, **123**, 231 (1921).

⁴³ Thierfelder and Schempp, *Arch. ges. Physiol.*, **167**, 280 (1917).

These biochemical methods, though of great physiological importance, obviously possess certain limitations from the practical standpoint of obtaining both *d*- and *l*-forms. Dilute solutions must be employed; hence the amounts which can be obtained are limited. It is necessary to find microorganisms or enzymes which destroy the *d*-form in one case and the *l*-form in another in order to secure both antipodes, and then at most only half the material is obtainable in an active state. Unlike method (c) and its variations, this method therefore finds little use.

4. Interconversion of Enantiomorphs. The Walden Inversion

The conversion of a *dextro* compound into its *levo* isomeride may be accomplished by means of a sequence of reactions which result in the exchange of two groups. An example of such an interconversion of optical isomers is Fischer's transformation⁴⁴ of the *dextro* form of the half amide of isopropylmalonic acid into its *levo* isomer, which has already been discussed (p. 226).

Another method of interconversion was discovered as the result of studies of the reactions of optically active compounds. The replacement of a group directly attached to an asymmetric carbon atom, such as *a* in Fig. 1, by a different group, *x*, may take place with no change in the

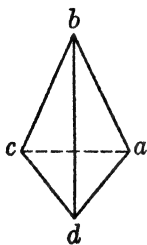


FIG. 1

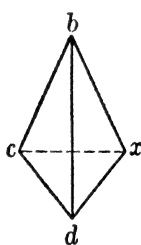


FIG. 2

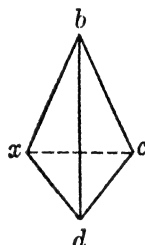


FIG. 3

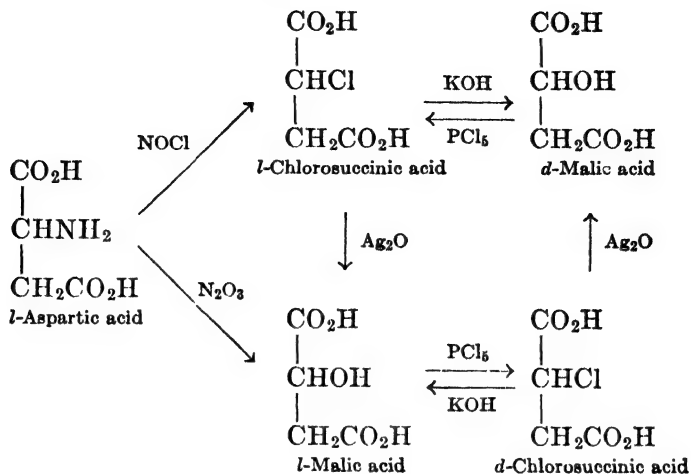
configuration of the groups about the asymmetric carbon atom. This leads to the formation of a compound represented by Fig. 2. However, it is known that in many reactions a change in configuration occurs and the product is the enantiomorph, Fig. 3. This phenomenon is known as the *Walden inversion*, since it was discovered by Paul Walden⁴⁵ in 1893.

As one illustration of these inversions, the following cycle of reactions⁴⁶ may be considered.

⁴⁴ Fischer and Brauns, *Ber.*, **47**, 3181 (1914).

⁴⁵ Walden, *Ber.*, **26**, 210 (1893); **29**, 133 (1896).

⁴⁶ Walden, *Ber.*, **32**, 1855 (1899); "Salts, Acids, and Bases: Electrolytes: Stereochemistry," McGraw-Hill Book Co., New York (1929).



Examination of the above cycle of transformations shows that *l*-aspartic acid produces *l*-malic acid by the direct action of nitrous anhydride, but that successive action of nitrosyl chloride and potassium hydroxide results in *d*-malic acid. This cycle of reactions also enables *l*-malic acid to be transformed into *d*-malic acid (and vice versa) by either of two routes. Likewise, *l*-chlorosuccinic acid and *d*-chlorosuccinic acid may be interconverted. Thus, by the choice of the proper sequence of reactions, using selected inorganic reagents, it is possible to convert a *dextro* compound into its *levo* isomer (and vice versa) without its passing through the racemic form.

Since the actual observed rotation does not reveal whether the resulting molecule has the same or a different configuration, it is impossible to state the exact steps in the cycle in which the inversion occurs.

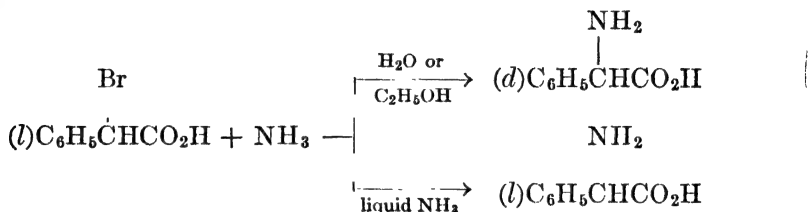
The contrast between the Walden inversion and racemization lies in the fact that in racemization only 50 per cent of the starting isomer is converted into its mirror image, and the product is racemic. Resolution is necessary in order to obtain the optical enantiomorph of the original. Since the Walden inversion produces the optically active enantiomorph, however, no resolution is necessary. In many cases, the conversion is nearly quantitative, and hence this method of interconverting optical isomers is sometimes useful for the preparation of certain optically active forms. The process, however, has its limitations in that it occurs *only when a group directly attached to an asymmetric carbon atom is replaced*. Moreover, partial racemization during the reactions may cause difficulty in isolating the pure optical isomer.

The investigations which have been conducted on the Walden inversion have shown that there are numerous factors which determine

whether or not an inversion will occur. Some of these factors are discussed below.

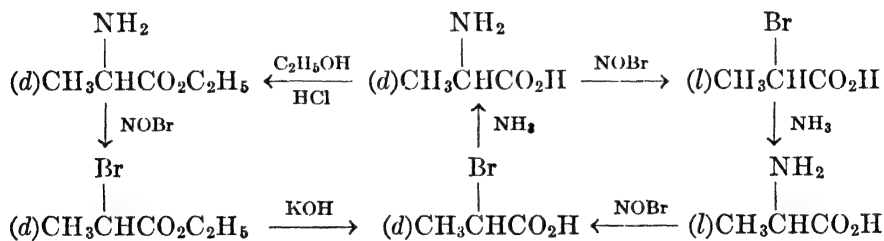
(a) **Nature of the Reagent.** The particular reagent chosen to effect a reaction exerts a predominating influence on the configuration of the product. This is illustrated in the reactions given above. It is evident that potassium hydroxide and silver oxide react in a different manner with the *d*- or *l*-chlorosuccinic acid.

(b) **Nature of the Solvent.**⁴⁷ The action of ammonia on *l*- α -bromophenylacetic acid produces either the *d*- or *l*-amino acid, according to

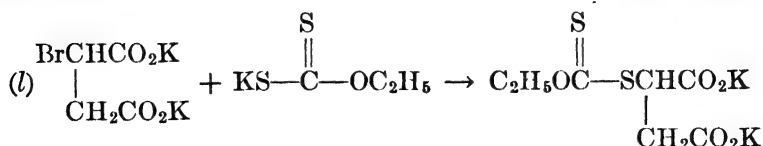


whether the reaction is carried out in water, alcohol, acetonitrile, or liquid ammonia.

(c) **Nature of the Compound.** Fischer⁴⁸ showed that the action of nitrosyl bromide on *d*-alanine produced *l*- α -bromopropionic acid, whereas the ethyl ester of *d*-alanine with the same reagent gave the ethyl *d*- α -bromopropionate. The latter hydrolyzed to *d*- α -bromopropionic acid. Thus, an inversion takes place in the case of the free acid, but does not when the ester is used. The cycle of changes which relate the isomeric forms of alanine, α -bromopropionic acid, and their esters is summarized in the following scheme.



(d) **Temperature.** Holmberg⁴⁹ determined the optical rotations of the xanthogensuccinic acid produced when the following reaction was



⁴⁷ Senter and others, *J. Chem. Soc.*, **107**, 638 (1915); **109**, 1091 (1916); **113**, 140, 151 (1918); **125**, 3137 (1924); **127**, 1847 (1925).

⁴⁸ Fischer, *Ber.*, **40**, 489, 502, 1052 (1907); Fischer and Schoeller, *Ann.*, **357**, 11 (1907)

⁴⁹ Holmberg, *Ber.*, **47**, 167 (1914).

carried out at different temperatures. The rotations obtained were:

| TEMPERATURE | SPECIFIC ROTATION |
|-------------|-------------------|
| 0° | +30.6° |
| 12 | + 8.3 |
| 25 | -13.8 |
| 40 | -40.1 |

It is evident that, in this reaction, temperature is an important factor in determining whether or not a Walden inversion takes place.

(e) **Absolute Configuration.** The prefixes *d*- and *l*- in the preceding and following discussion indicate the *direction* of rotation only and do not supply any information about the absolute configuration of the compounds. It should be clearly understood that a mere change in direction of rotation is not proof that an inversion has taken place. However, if an optically active compound is converted by means of selected reagents into the *d*- and *l*-forms of a new compound, or if a complete cycle of changes of a pair of optical isomers has been worked out, it is clear that an inversion must have taken place during one of the reactions.

In order to establish the exact step in which an inversion has occurred it is desirable to have some absolute method of establishing the configuration of each molecule independent of the reaction or observed rotation. This problem has been attacked by Boys,⁵⁰ who has developed an equation for calculating the magnitude of rotation as well as its direction for a simple molecule containing one asymmetric carbon atom attached to four different simple groups. The equation is:

$$[\alpha] = \frac{\left\{ 16.62(n^2 + 2)(n^2 + 5) \cdot R_A \cdot R_B \cdot R_C \cdot R_D \cdot (1 + F)(a - b) \right.}{(a - c)(a - d)(b - c)(b - d)(c - d)} \left. \right\}}{\lambda^2 \cdot M \cdot (a + b + c + d)^{14}}$$

where n = refractive index of medium in which rotation is measured.

$R_A, R_B, R_C,$ and R_D = refractivities of the groups $A, B, C,$ and D
as determined from Eisenlohr's tables.

a, b, c, d = radii of the groups in Ångström units.

F = a function of $a, b, c,$ and d .

λ = wavelength of light used.

M = molecular weight.

Thus, the specific rotation at a chosen wavelength is calculated from data on the radii of the four groups, molecular weight, and refractivities.

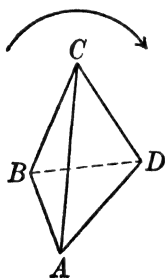
⁵⁰ Boys, *Proc. Roy. Soc. (London)*, [A] **144**, 655, 675 (1934).

The values calculated for simple compounds are of the same order of magnitude as those observed. For example:

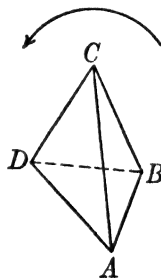
| | α_D CALCD. | α_D OBSERVED |
|---|-------------------|---------------------|
| $\text{CH}_3\text{CHOHC}_2\text{H}_5$ | 9.3° | 13.9 |
| $\text{CH}_3\text{CHNH}_2\text{C}_2\text{H}_5$ | 7.4 | 7.4 |
| $\text{CH}_3\text{CHC}_2\text{H}_5$ CH_2OH | 4.0 | 5.9 |
| $\text{CH}_3\text{CHC}_2\text{H}_5$ CH_2NH_2 | 3.6 | 5.8 |

The relative radii of the groups A , B , C , and D can be used with this equation to establish a relationship between the direction of rotation and spatial distribution. The value of $[\alpha]$ will be positive when the difference factors, i.e., $(a - b)$, $(a - c) \cdots$ etc., in the above equation are positive: this means that $A > B > C > D$. The rule stated by Boys is that a *dextro* compound has a configuration such that, when the largest group is nearest the observer, the other groups are arranged in order of diminishing size in a clockwise direction.

Thus, in a molecule C_{ABCD} , if A is the largest group and $B > C > D$ the *dextro* model would be that shown in Fig. 4, and the *levo* model would be that shown in Fig. 5.



dextro
FIG 4

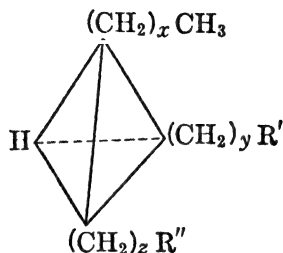


levo
FIG. 5

This empirical calculation of Boys has certain limitations but does offer a start in establishing configurations by measurement of radii of groups and their refractivities. It has not been widely used, and further work is necessary to establish its validity.

(f) **Rotatory Dispersion.** A second method for the correlation of structure and optical activity consists in studying the rotatory dispersion

of large numbers of closely related compounds. This has been done by Kuhn,⁵¹ Pickard and Kenyon,⁵² and especially by Levene⁵³ and his co-workers. Data have been obtained on a large number of compounds with the general formula:



where x , y , and $z = 0, 1, 2, 3$, etc.

R' = a functional group such as $-\text{OH}$, $-\text{X}$, $-\text{COOH}$,
 $-\text{NH}_2$, $-\text{CN}$.

$R'' = \text{CH}_3$, *iso*- C_3H_7 , C_6H_5 , C_6H_{11} .

All the compounds studied possess only one asymmetric carbon atom, and their rotatory dispersion curves have been measured over a range sufficiently large to permit an estimation of the partial rotations contributed by the groups attached to the asymmetric carbon atom.

The optical rotation of the molecule as a whole is the algebraic sum of the partial rotations of each of the four substituents. Thus by synthesizing a considerable number of the members of each of the homologous series represented by the above general formula and analyzing the rotatory dispersion curves it has been possible to relate the configurations of these molecules with their direction of rotation. From the data on optical rotations of related compounds Marker⁵⁴ has suggested an empirical method for predicting the configuration of optically active compounds.

(g) **Mechanism.** A third method for relating configuration with direction of rotation consists in obtaining some precise information concerning the mechanisms of reactions, particularly substitution reactions. During the past five years a considerable amount of fairly reliable information on certain of these points has been established.

⁵¹ Kuhn and Bein, *Z. physik. Chem.*, **B22**, 406 (1933); Kuhn, *ibid.*, **B31**, 23 (1936); Kuhn and Biller, *ibid.*, **B29**, 1 (1935).

⁵² Pickard and Kenyon, *J. Chem. Soc.*, **99**, 45 (1911); **105**, 830 (1914); Kenyon and Barnes, *ibid.*, **125**, 1395 (1924).

⁵³ Levene and co-workers, *J. Biol. Chem.* (1924-1936); Levene and Rothen, *J. Org. Chem.*, **1**, 76 (1937). See Gilman, "Organic Chemistry," John Wiley and Sons, New York (1938), 1st Edition, Vol. II, p. 1803 ff.

⁵⁴ Marker, *J. Am. Chem. Soc.*, **58**, 976 (1936).

Various mechanisms have been advanced to explain how an inversion of configuration can take place in some reactions but not in others.

1. According to the earlier investigators⁵⁵ complex addition compounds were produced. The position taken by a substituting group depended on the direction of the residual valencies of the asymmetric carbon atom and the nature of the displaced group.

2. Rördam⁵⁶ has assumed that, after one of the radicals has been removed from the asymmetric carbon atom, the position taken by the entering group depends on the phase of oscillation of the three radicals remaining. The form which has the same configuration as the original is the one whose proportion increases as the concentration of the reagent increases.

3. The possibility that the replacement of a group involves a preliminary or incipient ionization process induced by the reagents or solvents has been considered by a number of workers.⁵⁷ The phenomenon of the Walden inversion is very closely connected with the mechanism of substitution reactions in general, and intensive investigations are now being carried out in order to establish the unimolecular, bimolecular, or polymolecular character of solvolytic reactions which involve replacement.⁵⁸ Excellent reviews of this subject have been contributed by Watson⁵⁹ and by Hammett.⁶⁰

4. An acceptable mechanism for the Walden inversion not only must show how the configuration of the asymmetric carbon atom is inverted but also must provide a reasonable explanation as to *why racemization is not the exclusive process*. One of the best solutions of this enigma is the suggestion of G. N. Lewis⁶¹ that a substitution reaction takes place by *simultaneous* addition of one group and removal of the other. This idea has been elaborated by Olson,⁶² who has made the suggestion, supported by experimental evidence,⁶³ that a one-step sub-

⁵⁵ Fischer, *Ann.*, **381**, 123 (1911); Werner, *Ber.*, **44**, 873 (1911); Pfeiffer, *Ann.*, **383**, 123 (1911); Frankland, *J. Chem. Soc.*, **103**, 713 (1913); Meisenheimer, *Ann.*, **456**, 126 (1927).

⁵⁶ Rördam, *J. Chem. Soc.*, 2447 (1928); 1282 (1929); 2017 (1930); Levene and Walti, *J. Biol. Chem.*, **73**, 263 (1927); Levene and Rothen, *ibid.*, **81**, 359 (1929).

⁵⁷ Lowry, *Deuxième Conseil de Chimie Solvay*, 1925, p. 174; Kenyon and Phillips, *Trans. Faraday Soc.*, **26**, 451 (1930); Ingold *et al.*, *J. Chem. Soc.*, 236 (1935); *ibid.*, 1196, 1201, 1208, 1252 (1937).

⁵⁸ Stiegman and Hammett, *J. Am. Chem. Soc.*, **59**, 2536 (1937); Farinacci and Hammett, *ibid.*, **59**, 2542 (1937); Olson and Halford, *ibid.*, **59**, 2644 (1937); Taylor, *J. Chem. Soc.*, 1853 (1937); Bartlett, *J. Am. Chem. Soc.*, **61**, 1630 (1939); Winstein, *ibid.*, **61**, 1635 (1939).

⁵⁹ Watson, *Ann. Repts. Chem. Soc. (London)*, **35**, 208 (1938).

⁶⁰ Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York (1940).

⁶¹ Lewis, "Valence and the Structure of Atoms and Molecules," Chemical Catalog Co., New York (1923), p. 113.

⁶² Olson, *J. Chem. Phys.*, **1**, 418 (1933).

⁶³ Olson and Long, *J. Am. Chem. Soc.*, **56**, 1294 (1934); Olson and Voge, *ibid.*, **56**, 1690 (1934).

stitution reaction leads to inversion of configuration. As an example to illustrate this simultaneous or synchronous mechanism of substitution, one of the possible modes* of the action of hydrobromic acid on *d*-octanol-2 may be considered.

The alcohol is shown in Fig. 6, in which the asymmetric carbon atom is represented by the tetrahedron. The alcohol probably forms the oxonium salt with the proton, and the bromide ion then approaches the face of the tetrahedron opposite to the apex at which the hydroxyl was attached, Fig. 7. This particular mode of approach is determined

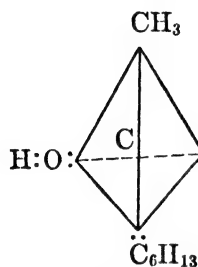


FIG. 6

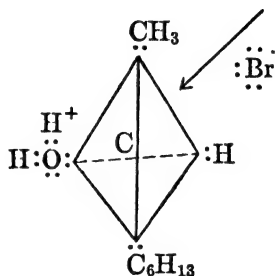


FIG. 7

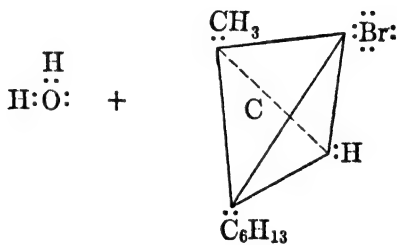


FIG. 8

by the character of the hydroxyl group, and calculations ^{62, 64} have shown that such orientation of the reactants constitutes a unique path for the entering group because this requires less energy than would be necessary for approach in any other direction. At the instant the bromide ion occupies the proper position for the formation of a new tetrahedron, the molecule of water is expelled and the kernel of the asymmetric carbon atom shifts its position, establishing the new tetrahedron as shown in Fig. 8. The molecule is turned inside out like an umbrella in a strong wind. A comparison of the model of Fig. 8 with that of Fig. 6 shows that

* There are also other mechanisms for the reaction between alcohols and halogen acids see Hammett, Ref. 60.

⁶⁴ Pauling, *ibid.*, **53**, 1367 (1931); Slater, *Phys. Rev.*, **37**, 481 (1931).

the bromine does *not* occupy the same position as the hydroxyl group and that an inversion in configuration has occurred.

It is not necessary that the reagent be ionic. For example, the same mechanism applies to the conversion of *d*- α -phenylethyl chloride (Fig. 9) by ammonia in a non-polar solvent via the oriented approach shown in Fig. 10, into the hydrochloride of *l*- α -phenylethylamine (Fig. 11). An inversion in configuration has thus taken place.

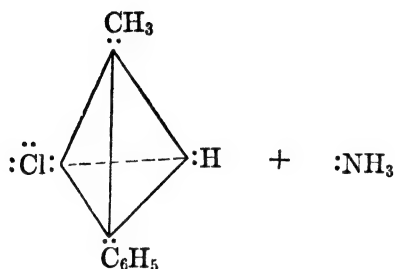


FIG. 9

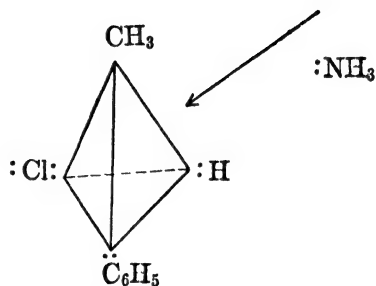


FIG. 10

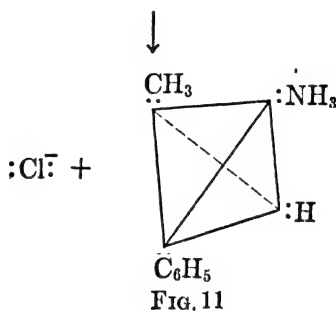
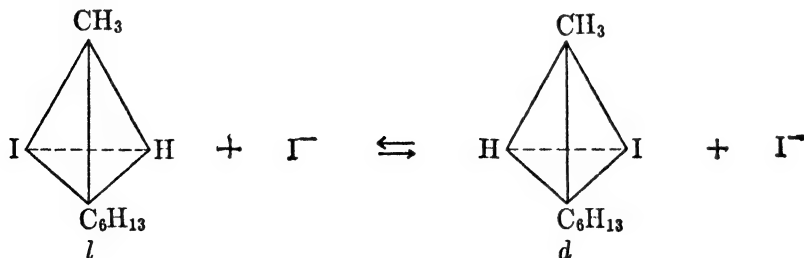


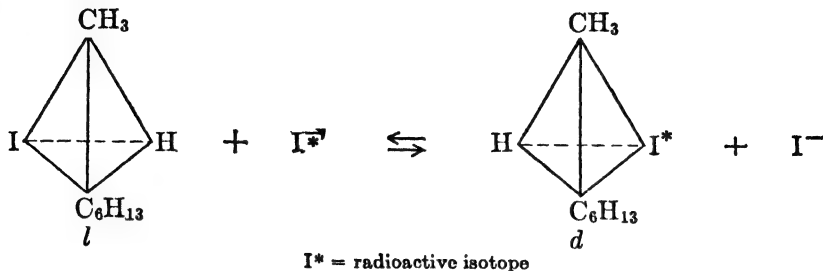
FIG. 11

If an optically active iodide such as *l*-2-iodooctane is treated with sodium iodide in acetone solution it is found that racemization takes

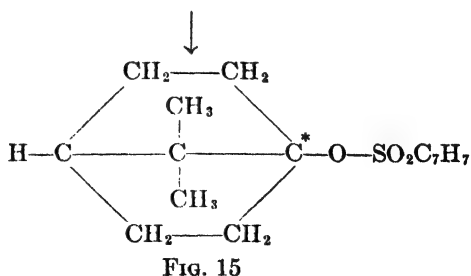
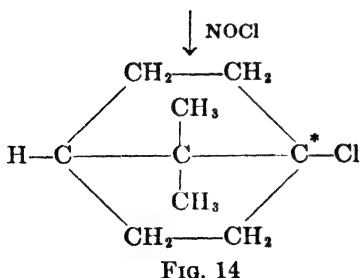
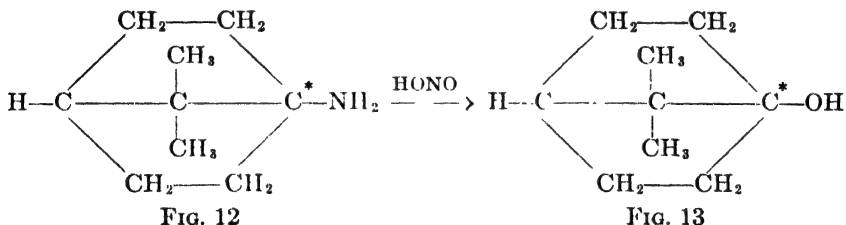


place. The iodide ion has reacted by approaching the face opposite the iodo group to produce *d*-2-iodooctane, and at equilibrium the racemic modification results. By using sodium iodide containing the radioactive

isotope of iodine the rate of exchange of halogen may be determined for the reaction.



Measurements of the intensities of radioactivity of the alkyl halide or sodium iodide are made at definite time intervals. At the same time the velocity of racemization is followed polarimetrically, and it was found ⁶⁵ that the rates of exchange and of racemization were equivalent within experimental error. Similar experiments on α -phenylethyl bromide ⁶⁶ and α -bromopropionic acid ⁶⁷ gave analogous results and established the fact that inversion occurs when a halide ion displaces another group which forms an anion. Meer and Polanyi ⁶⁸ have also contributed evidence on these anionic replacement reactions; they further point out that attack of a molecule by a cation would probably not lead to inversion although such reactions have not been thoroughly characterized as yet. Further proof of this rearward attack by anionic reagents has been obtained by a study of the compounds shown in Figs. 12, 13, 14, and 15.



⁶⁵ Hughes, Juliusburger, Masterman, Topley, and Weiss, *J. Chem. Soc.*, 1525 (1935).

⁶⁶ Hughes, Juliusburger, Scott, Topley, and Weiss, *ibid.*, 1173 (1936).

⁶⁷ Cowdrey, Hughes, Nevell, and Wilson, *ibid.*, 209 (1938).

⁶⁸ Meer and Polanyi, *Z. physik. Chem.*, B19, 164 (1932); Polanyi, "Atomic Reactions," Williams & Norgate, Ltd., London (1932), p. 63.

The starred carbon atom in these molecules has the tetrahedral face opposite the functional group inside a cage of carbon atoms and hence is inaccessible to the approach of any reagent. Therefore, anionic replacement by the mechanism described above is impossible. It was actually found by Bartlett and Knox ⁶⁹ that the tertiary alcohol apocamphanol-1 (Fig. 13) was not oxidized by dichromate, not dehydrated or rearranged by concentrated sulfuric acid, and could not be converted to the chloride (Fig. 14) by the action of phosphorus pentachloride or thionyl chloride. The chlorine in 1-chloroapocamphane (Fig. 14), prepared by the action of nitrosyl chloride on the amine (Fig. 12), could not be removed by boiling alcoholic sodium ethoxide or silver nitrate. The *p*-toluenesulfonate (Fig. 15) was unaffected by boiling with an acetone solution of lithium iodide. Thus, all attempts to replace the hydroxyl or chloro group by anionic reagents failed. It is inferred that the replacement reactions of the amino group by hydroxyl with nitrous acid, and by chlorine with nitrosyl chloride, must occur by mechanisms not involving the rearward anionic mechanism. Bartlett and Cohen ⁷⁰ have also demonstrated that the bromine in the molecule represented by Fig. 16 is quite inert whereas that in 9-bromo-9-methylfluorene (Fig. 17) is quite reactive.

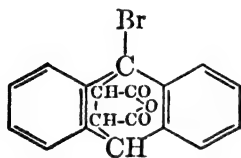


FIG. 16

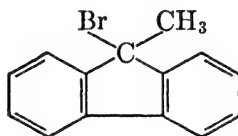
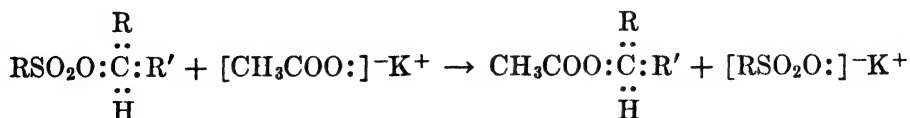


FIG. 17

The optically active esters of the sulfonic acids constitute a class of compounds especially suited for determining the effect of anion exchange on optical activity. Phillips, Kenyon,⁷¹ and their co-workers, by treatment of an optically active ester of a sulfonic acid with ionic reagents such as potassium acetate, demonstrated that the sulfonate radical may be replaced by another anion. Ammonia and primary and secondary

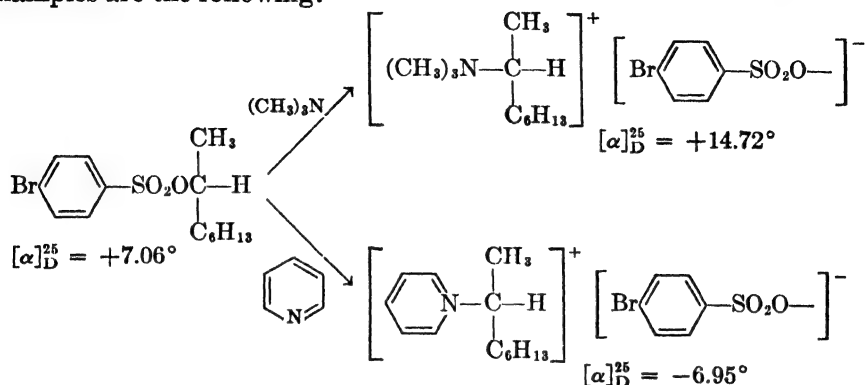


⁶⁹ Bartlett and Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939)

⁷⁰ Bartlett and Cohen, *ibid.*, **62**, 1183 (1940).

⁷¹ Phillips, *J. Chem. Soc.*, **123**, 44 (1923); Kenyon, Phillips, and Turley, *ibid.*, **127**, 399 (1925); Phillips, *ibid.*, **127**, 2552 (1925); Kenyon and Phillips, *ibid.*, 1676 (1930); *Trans. Faraday Soc.*, **26**, 451 (1930); Kenyon, Phillips, and Pittman, *J. Chem. Soc.*, 1072 (1935); Kenyon, Phillips, and Shutt, *ibid.*, 1663 (1935).

amines were also found to react with such esters to produce optically active amines. Tertiary amines react with optically active alkyl sulfonates to produce optically active quaternary ammonium salts.⁷² Two examples are the following:



From the above, it will be noted that the *dextro* ester produces a *dextro* quaternary salt with trimethylamine, but a *levo* pyridinium salt. Also, the *levo* ester yields *levo*-trimethyl-2-octylammonium-*p*-bromobenzenesulfonate, but a *dextro* pyridinium salt. A Walden inversion probably occurs during at least one of these reactions. The tertiary amine approaches the ester in an oriented position, such that the unshared pair of electrons at one apex is opposite that face of the asymmetric carbon atom which, in turn, is opposite the sulfonate group (Fig. 18).

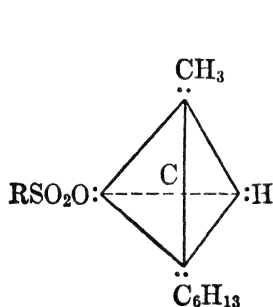


FIG. 18

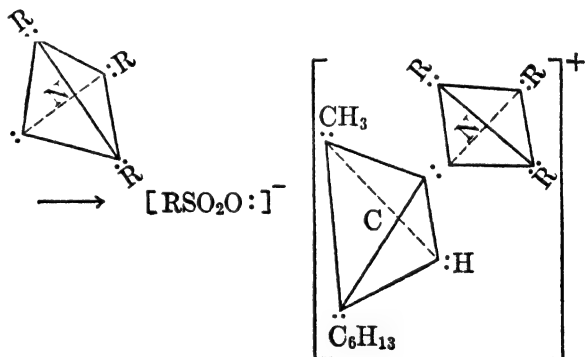


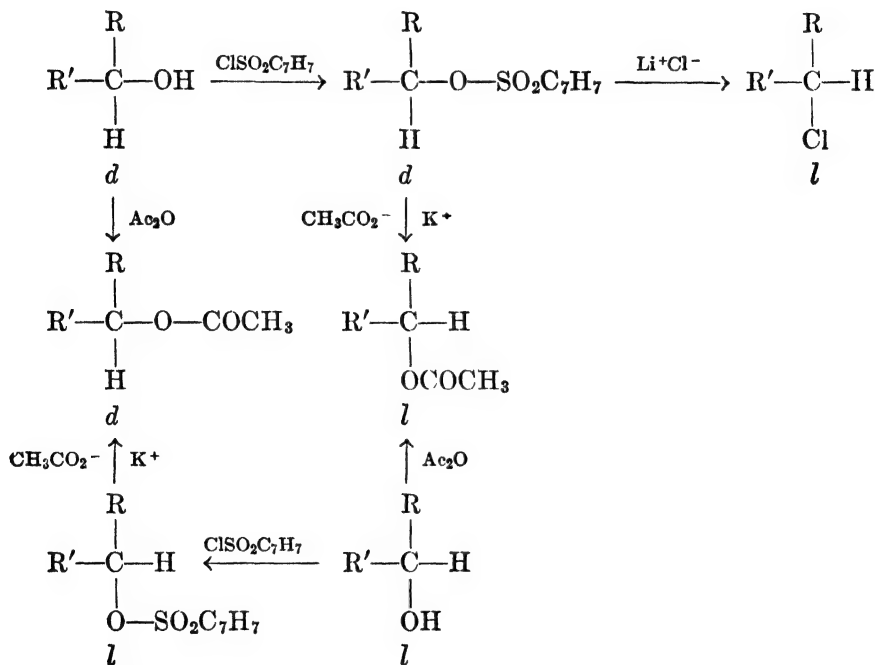
FIG. 19

The kernel of the carbon atom shifts its position and a new tetrahedron is formed attached to the tetrahedron of the nitrogen atom, thus constituting the quaternary ammonium ion and simultaneously the sulfonate anion (Fig. 19). If the amine approaches the face indicated, then an inversion in configuration takes place. If, however, the amine

⁷² Cary, Vitcha, and Shriner, *J. Org. Chem.*, **1**, 280 (1936).

approaches any of the other three faces, the sulfonate ion could be displaced without inversion. Since there is no independent means of establishing the configuration of these quaternary salts it is not possible to say whether a Walden inversion occurs in both cases.

By using anionic exchange reactions which lead to inversion, in conjunction with reactions which do not cause inversion since the reagents do not react with a group directly attached to the asymmetric carbon atom, Kenyon and Phillips⁷³ have been able to establish configurational relationships of derivatives of octanol-2, α -benzylethyl alcohol,⁷⁴ α -phenylethyl alcohol,⁷⁵ ethyl lactate,⁷⁶ and ethyl β -hydroxy- β -phenylpropionate.⁷⁷ The following scheme summarizes one of the general procedures used in this work.



Studies on the mechanism of formation of esters from alcohols⁷⁸ have established beyond doubt that these reactions do not involve the carbon-oxygen link in the alcohol and hence such reactions cannot cause inver-

⁷³ Phillips, *J. Chem. Soc.*, **123**, 44 (1923); Houssa, Kenyon, and Phillips, *ibid.*, 1700 (1929).

⁷⁴ Phillips, *ibid.*, **123**, 44 (1923).

⁷⁵ Kenyon, Phillips, and Taylor, *ibid.*, 173 (1933).

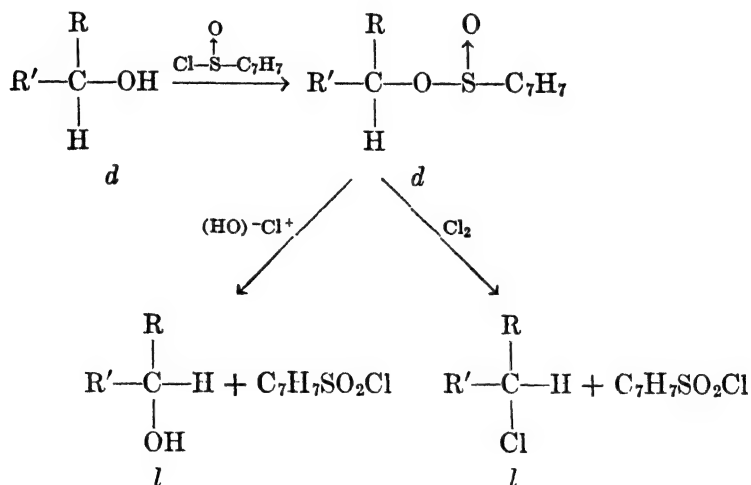
⁷⁶ Kenyon, Phillips, and Turley, *ibid.*, **127**, 399 (1925).

⁷⁷ Kenyon, Phillips, and Shutt, *ibid.*, 1663 (1935).

⁷⁸ Waters, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., New York (1937).

sion. Hence the *d*-acetate and the *d*-*p*-toluenesulfonate have the same configuration as the *d*-alcohol from which they are derived. Likewise the *l*-alcohol, *l*-acetate, and *l*-*p*-toluenesulfonate are configurationally related. The action of potassium acetate on the *p*-toluenesulfonates, however, involves an anionic exchange and therefore leads to inversion. Thus the acetate obtained by this method has the opposite configuration and opposite rotation from that obtained by direct esterification.

If the chloride and acetate ions react with the ester in a similar fashion then an inversion also takes place when the *d*-*p*-toluenesulfonate reacts with lithium chloride and therefore the *l*-chloride has a configuration opposite to that of the *d*-alcohol but the same as that of the *l*-alcohol. Similar conclusions were drawn from observations on the replacement of the sulfinate group.



The sulfinic ester has the same configuration as the alcohol from which it is derived (at least as far as the asymmetric carbon atom is concerned; no information concerning the asymmetric sulfur atom is available). The negative hydroxyl ion produces the *l*-alcohol, and chlorine the *l*-chloride, and both of these are anionic replacements and hence involve inversion.

These investigations of Kenyon and Phillips, therefore, not only serve to establish relative configurations but also furnish further evidence for inversion in reactions involving anionic exchange.

Once a series of relative configurations has been established, it is possible to use such compounds to establish the behavior of other reagents. For example, phosphorus pentachloride or trichloride converts

*be *d*-alcohol into the *l*-chloride. Since the above transformations indicate that the *l*-chloride has the opposite configuration to the *d*-alcohol, it follows that these reagents cause inversion.

A list of relative configurations was drawn up by Frankland ⁷⁹ in 1913 on the basis of a purely statistical survey of the reactions recorded in the literature on the behavior of various reagents. Recent work has confirmed and added to the list.

Cowdrey, Hughes, Ingold, Masterman, and Scott ⁸⁰ have summarized the configurational relationships between certain groups of compounds. These relationships were established by studying the optical effect of substitution on an asymmetric carbon atom and paralleling these observations by kinetic studies and correlating the results with the data obtained on the mechanism of substitution reactions in general. A summary of the configurationally related compounds follows:

2-Octyl Derivatives: *d*-chloride, *d*-bromide, *d*-alcohol, *d*-ethyl ether, *d*-acetate.

α-Phenylethyl Derivatives: *d*-chloride, *d*-bromide, *d*-alcohol, *d*-methylether, *d*-amine.

α-Substituted Propionic Acids: *d*-chloro, *d*-bromo, *d*-iodo, *d*-methoxy, *l*-hydroxy (*l*-lactic acid).

α-Substituted β-Phenylpropionic Acids: *d*-chloro, *d*-bromo, *d*-hydroxy.

α-Substituted Phenylacetic Acids: *d*-chloro, *d*-bromo, *d*-methoxy, *d*-hydroxy (*d*-mandelic acid).

α-Substituted α-Phenylpropionic Acids: *d*-chloro, *d*-hydroxy.

β-Substituted n-Butyric Acids: *d*-chloro, *d*-hydroxy.

β-Substituted β-Phenylpropionic Acids: *d*-chloro, *d*-bromo, *d*-hydroxy.

Substituted Succinic Acids: *d*-chloro, *d*-bromo, *d*-iodo, *d*-malic, *d*-malolactonic.

2-Butyl Derivatives: *d*-hydroxy, *d*-chloride, *d*-bromide, *d*-iodide.

2-Pentyl Derivatives: *d*-hydroxy, *d*-iodide, *d*-chloride.

α-Phenyl-n-Propyl Derivatives: *d*-hydroxy, *d*-chloride, *d*-bromide.

α,α'-Disubstituted Succinic Esters: *d*-methyl tartrate, *d*-ethyl tartrate, *d*-methyl and *d*-ethyl chloromalate, *d*-ethyl bromomalate.

2-Hexyl Derivatives: *d*-hydroxy, *d*-chloride.

3-Nonyl Derivatives: *d*-hydroxy, *d*-chloride, *d*-bromide, *d*-iodide.

The reagents may also be classified along with the reactants into groups according to whether or not inversion is produced (see p. 279).

In addition to the results involving anionic attack discussed in the foregoing pages, a second type obtaining its driving force from an attack by a cation may also lead to an inversion in configuration. This may be illustrated by the alkylation of benzene with *d*-butanol-2 in the presence of boron fluoride,⁸¹ which yielded about 0.5 per cent *l*-2-phenylbutane and 99.5 per cent of the *dl*-modification.

⁷⁹ Frankland, *J. Chem. Soc.*, **103**, 713 (1913).

⁸⁰ Cowdrey, Hughes, Ingold, Masterman, and Scott, *ibid.*, 1252 (1937).

⁸¹ Price and Lund, *J. Am. Chem. Soc.*, **62**, 3105 (1940); Burwell and Archer, *J. Am. Chem. Soc.*, **64**, 1032 (1942).

I. INVERSION OF CONFIGURATION OCCURS:

| Reagent | Reactant |
|--|--|
| PCl_3 | Octanol-2, α -phenylethyl alcohol, ethyl β -hydroxy- β -phenylpropionate |
| $\text{PCl}_3 + \text{C}_6\text{H}_5\text{N}$ | α -Phenylethyl alcohol, ethyl β -hydroxy- β -phenylpropionate |
| POCl_3 | Octanol-2, α -phenylethyl alcohol |
| POCl_3 | α -Phenylethyl alcohol, methyl mandelate |
| PCl_5 or PBr_5 | Octanol-2, α -phenylethyl alcohol, lactic acid, ethyl lactate, malic acid, methyl malate, mandelic acid, methyl mandelate |
| $\text{PCl}_5 + \text{C}_6\text{H}_5\text{N}$ | Octanol-2, α -phenylethyl alcohol, ethyl lactate |
| SOCl_2 | Octanol-2, lactic acid, ethyl lactate, malic acid, ethyl malate |
| $\text{SOCl}_2 + \text{C}_6\text{H}_5\text{N}$ | Octanol-2, α -phenylethyl alcohol, ethyl lactate, ethyl mandelate |
| HCl | Pentanol-2, octanol-2, α -phenylethyl alcohol, α -phenyl- <i>n</i> -propyl alcohol |
| HBr | Butanol-2, octanol-2, α -phenylethyl alcohol, α -phenyl- <i>n</i> -propyl alcohol |
| HI | Octanol-2 |

II. SUBSTITUTION WITH RETENTION OF CONFIGURATION:

| Reagent | Reactant |
|-----------------|--|
| SOCl_2 | α -Phenylethyl alcohol, mandelic acid, methyl mandelate |

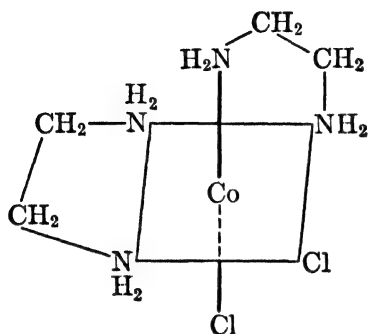
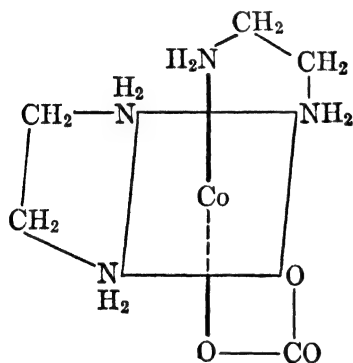
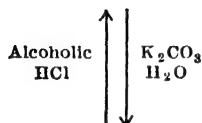
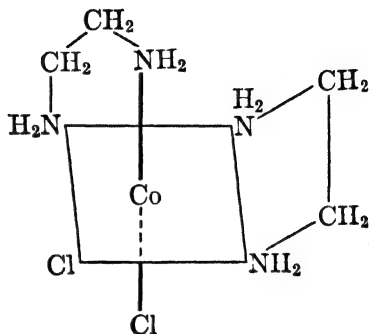
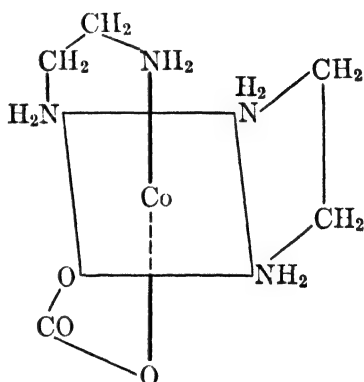
It has also been shown that an inversion of configuration takes place in certain complex compounds of cobalt⁸² (p. 437) which have an octahedral configuration. Thus, treatment of an aqueous solution of the *d-cis* complex ion of Fig. 20 with a solution of potassium carbonate produces the *d*-carbonato compound of Fig. 21. However, if the *d*-dichloro complex is ground with an excess of solid silver carbonate and a small amount of water is added, the *l*-isomer, Fig. 22, is produced. This is converted to the *l*-dichloro complex, Fig. 23, by alcoholic hydrochloric acid.

The configurations of the complex ions were assigned as the result of rotatory dispersion studies,⁸³ and hence the inversion is represented as taking place in the conversion of the *d*-dichloro complex (Fig. 20) to the

⁸² Bailar and Auten, *ibid.*, **56**, 774 (1934); Bailar, Jonelis, and Huffman, *ibid.*, **58**, 2224 (1936); Bailar, Haslam, and Jones, *ibid.*, **58**, 2226 (1936); Werner and McCutcheon, *Ber.*, **45**, 3284 (1912).

⁸³ Mathieu, *Bull. soc. chim.*, [5] **3**, 476 (1936); *ibid.*, [5] **4**, 687 (1937).

l-carbonato complex (Fig. 22). It is not yet certain whether the mechanism suggested for inversions of the tetrahedral carbon atom may be applied to the octahedral elements. Careful consideration of the models of these complex cobalt compounds shows that the *d*-isomer may be

FIG. 20 *d*-cisFIG. 21 *d*-cisFIG. 23 *l*-cisFIG. 22 *l*-cis

transformed to the *l*-isomer merely by exchanging the point of attachment of two groups—a structural change paralleling the *d*- and *l*-forms of the asymmetric carbon atom. Hence, it is possible that the configurations of these optically active cobalt complexes may be inverted by the proper oriented approach of the anion followed by establishment of a new optical configuration. Examination of the models of these compounds shows that this inversion does not necessitate the formation of a new octahedron.

In concluding this summary of investigations on the Walden inversion it must be emphasized that experimental conditions play a very important and determining role. Future investigations will serve to clarify many unsettled points on the mechanism of substitution reactions. Kinetic studies on the mechanism of substitution reactions are being made in an effort to provide a means of establishing the absolute configurations of optically active molecules. The results of these studies, together with the chemical information already at hand, will not only provide mechanisms for the Walden inversion with ionic and non-ionic reagents but will also markedly advance our knowledge of reaction mechanisms in general.

PART V. POLARIMETRY

Light. Until about 1900 the electromagnetic wave theory of light extensively developed by Maxwell was competent to give a satisfactory picture of the behavior of light and radiation phenomena in general. This theory was extremely useful in correlating and predicting exactly almost all the known facts concerning the interference, polarization, refraction, and reflection phenomena exhibited by light. However, starting about 1900, and extending up to the present time, a number of experimental observations on radiant energy have made it apparent that the classical wave theory would have to be modified.

For example, Planck and Einstein have shown that when light reacts with matter it does so as if it were composed of discrete particles known as corpuscles or photons. These photons possess an amount of energy equal to $h\nu$ (h = a universal constant = 6.55×10^{-27} erg sec. and ν = frequency), travel with the speed of light ($c = 3 \times 10^{10}$ cm. per sec.), and possess a momentum equal to $h\nu/c$ g.cm. per sec. This concept of the nature of light is necessary to explain photoeffects, black-body radiation, emission of line spectra, the Compton effect of x-rays, and the Raman effect.

It is of interest to point out that experiments have been performed in recent years which show that material particles behave, under certain conditions, as though they were a wave train. Davisson and Germer, and G. P. Thomson, have shown that a stream of electrons exhibits the phenomena of interference, diffraction, and refraction just as do ordinary light waves. By a study of diffraction patterns the "wavelength" of the electrons has been found to be $\lambda = h/p$ (h = Planck's constant and p is the momentum). This equation had been deduced previously by de Broglie, and a number of experiments have now shown that atoms as well as electrons apparently possess the properties associated with waves.

This interesting duality between waves and corpuscles has caused a revision of the classical mechanics and led to the development of the new wave mechanics—or quantum mechanics.

Thus, both light and material particles seem to possess a dual nature. As far as light is concerned, although it may be composed of discrete units of energy and although the exact path of any one of these photons cannot be predicted with certainty, nevertheless the *paths* followed *on the average* by a large number of them, as in a beam of light, may be predicted by the laws governing waves. It is, therefore, still a *wave theory* which predicts and describes exactly the refraction and polarization effects exhibited by light rays, and this viewpoint will be used in the following discussion.

Ordinary white light may be regarded as a mixture of waves of different lengths, the resultant vibrations being at right angles to the direction of propagation and the trains of waves making up a beam of light having different planes of vibration. By proper choice of the light source or the use of suitable filters, light waves of a single wavelength may be obtained. Such light is called *monochromatic*.

Plane-Polarized Light. The waves in a beam of monochromatic light vibrate at random. A cross section of such a beam traveling perpendicular to the paper is shown in Fig. 1, which indicates that many

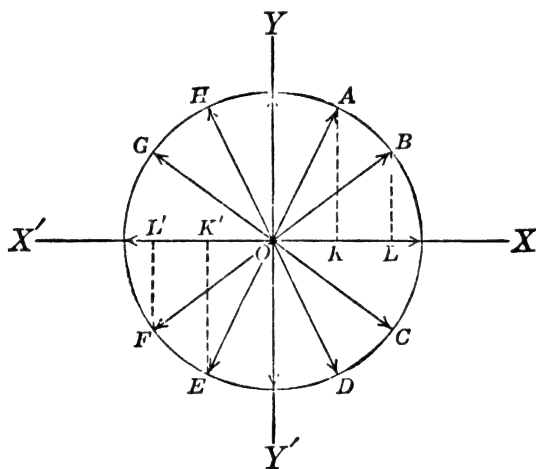


FIG. 1

planes of vibration are present. For example, *AOE*, *BOF*, *COG*, *DOH* represent projections of various waves on the paper. By reflection or refraction it is possible to sift out the component vibrating in a single plane. Thus, if the above beam of light is passed through a polarizer which transmits vibrations only along the *X'OX*-axis, the

entire wave represented by AOE cannot pass through, but only the horizontal component represented by OK and OK' will emerge. Similarly, for the wave BOF , the horizontal component OL and OL' will pass through the polarizer. The light emerging from such a polarizer will, therefore, vibrate along $X'OX$ and is said to be *plane polarized*.

The common method for obtaining plane-polarized light consists in passing the beam of light through a polarizer called a Nicol prism. This prism is made of calcite, a crystalline form of calcium carbonate, which possesses the power of causing double refraction. That is, an ordinary ray of light entering this calcite crystal is broken into two rays, one of which obeys the usual laws of refraction and is called the *ordinary ray*. The other ray, which is not refracted normally, is called the *extraordinary ray*. The light in each of these rays is found to be plane polarized, and the planes of polarization of the two rays are perpendicular to each other.

The Nicol prism is a device for rejecting one of these rays and transmitting the other. It is constructed by cutting a crystal of calcite diagonally and symmetrically through its obtuse corners, polishing the cut faces, and cementing them together again with a film of Canada balsam or linseed oil. The faces of the rhombohedron are polished so that the acute angle is 68° . A cross section through such a prism is shown in Fig. 2. The ray of light entering the prism at (A) is broken up into the

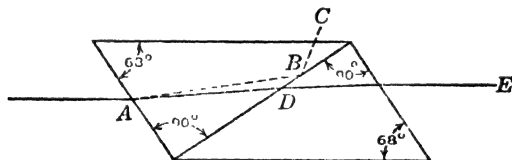


FIG. 2

ordinary ray (AB) and the extraordinary ray (AD). The cement between the two halves has a refractive index slightly less than that of calcite for the ordinary ray. The angles at which the prism is cut are adjusted so that the ordinary ray is completely reflected at the junction of the two halves of the Nicol prism while the extraordinary ray passes on through and is plane-polarized light.

Another device for polarizing light consists of a sheet of transparent material such as cellulose acetate in which are embedded large numbers of very small birefringent crystals. These crystals must be uniformly oriented optically so that the film behaves like a very thin single birefringent crystal.¹ The compounds used are: double salts of the alkaloids

¹ See Freundlich, *Chemistry & Industry*, 698 (1937), for a review of this subject.

such as quinine or cinchonine with sulfuric acid, hydriodic acid, and iodine; potassium nitrate; potassium dichromate; urea; or complex cobalt salts.¹ The practical development of these films was made by E. H. Land,² and the films are known as "Polaroid films." The films may be protected by lamination between two thin sheets of glass. The films absorb a considerable percentage (30 to 50 per cent) of light, but the transmitted light is said to be 98–99 per cent plane polarized in the range 5000 to 7000 Å. The Polaroid films have the advantage of furnishing much larger apertures than Nicol prisms. Polarimeters have recently been made using these Polaroid films.

The Polarimeter. The rotatory power which compounds exert on plane-polarized light is determined by means of an instrument called the polarimeter. A diagrammatic sketch of the essential working parts of the Lippich half-shadow polarimeter is shown in Fig. 3.

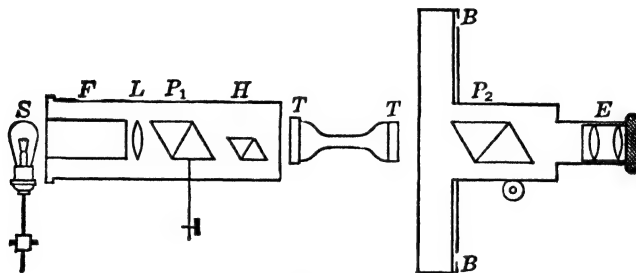


FIG. 3

Since the rotatory power exerted by a substance varies with the wavelength, a monochromatic source of light (*S*) is essential. The most satisfactory sources are:

1. The yellow sodium light produced by heating sodium salts to a high temperature or an electrically operated sodium-vapor lamp. These sources are often used alone, but a light filter (*F*) is necessary to get monochromatic light corresponding to the sodium D line ($\lambda = 5893 \text{ Å}$).
2. The green mercury light produced by a mercury arc with suitable filters at *F* ($\lambda = 5461 \text{ Å}$).
3. Light of other wavelengths may also be obtained from suitable helium, lithium, or cadmium lamps.

The monochromatic light is converted into a parallel beam by the lens (*L*) and enters the polarizing Nicol prism (*P*₁). The emergent plane-polarized light next meets a small Nicol prism (*H*) which covers half the field and is placed at a slight angle (1 to 4°) to the first Nicol

² E. H. Land, Brit. pats., 412,179 (1934); 423,874 (1935); 433,455 (1935); U. S. pats., 1,951,664 (1934); 1,955,923 (1934); 1,989,371 (1935); 2,041,138 (1935); 2,123,901 (1938); 2,123,902 (1938); 2,165,973 (1939); 2,165,974 (1939).

(P_1). This small Nicol prism creates a difference in intensity of light in the two halves of the beam and is often called the half-shadow Nicol prism. The difference in intensity is due to the fact that the light which emerges from this prism represents only that component of the original ray vibrating in the direction of transmission of the half-shadow Nicol. The beam next passes through the substance, whose optical properties are being studied, placed in the tube TT . The extent of rotation of the plane of the polarized light by the compound is determined by the analyzing Nicol prism P_2 which is mounted in a framework with scale B, B graduated in degrees and which may be rotated about the axis until the two halves of the field are of equal intensity. The lenses in the eyepiece, E , are used to secure a sharp focus on the line dividing the two fields. Verniers on the scales are used to obtain accurate readings. Rotations are determined by noting the difference in the readings obtained when the tube TT is empty and when filled with the compound.

The results are expressed as follows:

For pure compounds,

$$[\alpha]_{\lambda}^T = \frac{a}{l \cdot d}$$

where $[\alpha]_{\lambda}^T$ is the specific rotation at the temperature T , for light with the wavelength λ . The value a is the degrees of rotation observed in a tube l decimeters in length for a pure compound whose density is d .

For compounds in solution,

$$[\alpha]_{\lambda}^T = \frac{100a}{l \cdot g \cdot d} \quad \text{or} \quad [\alpha]_{\lambda}^T = \frac{100a}{l \cdot c}$$

where g is the grams of solute per 100 g. solution of density d , and c is the grams of solute per 100 cc. of solution.

Molecular rotations are calculated by multiplying the specific rotation by the molecular weight.

$$[M]_{\lambda}^T = [\alpha]_{\lambda}^T \cdot M$$

Since these molecular rotations are likely to be large numbers, one one-hundredth of this value is sometimes given. The specific rotation is dependent upon and varies with (1) the nature of the compound, (2) the nature of the solvent, (3) the wavelength of light, and (4) the temperature.

Circularly Polarized Light. Plane-polarized light is the type of polarized light which has been most widely used in the study of optical isomerism. However, some interesting and fundamental data have been secured by means of circularly polarized light.

The nature of circularly polarized light may be understood best by

resolving it into its components. Figure 4 shows two waves of plane-polarized light traveling in the same direction whose planes of vibration

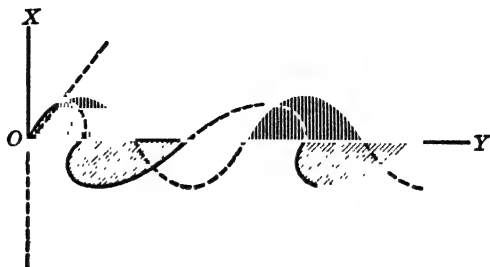


FIG. 4

are at right angles to each other. The waves also have a one-quarter-wavelength (90°) phase difference and equal amplitudes.

The resultant of these waves, obtained by adding vectorially the displacements at all points along OY , is *circularly polarized light* represented by the spiral in the photograph, Fig. 5. In the illustration the

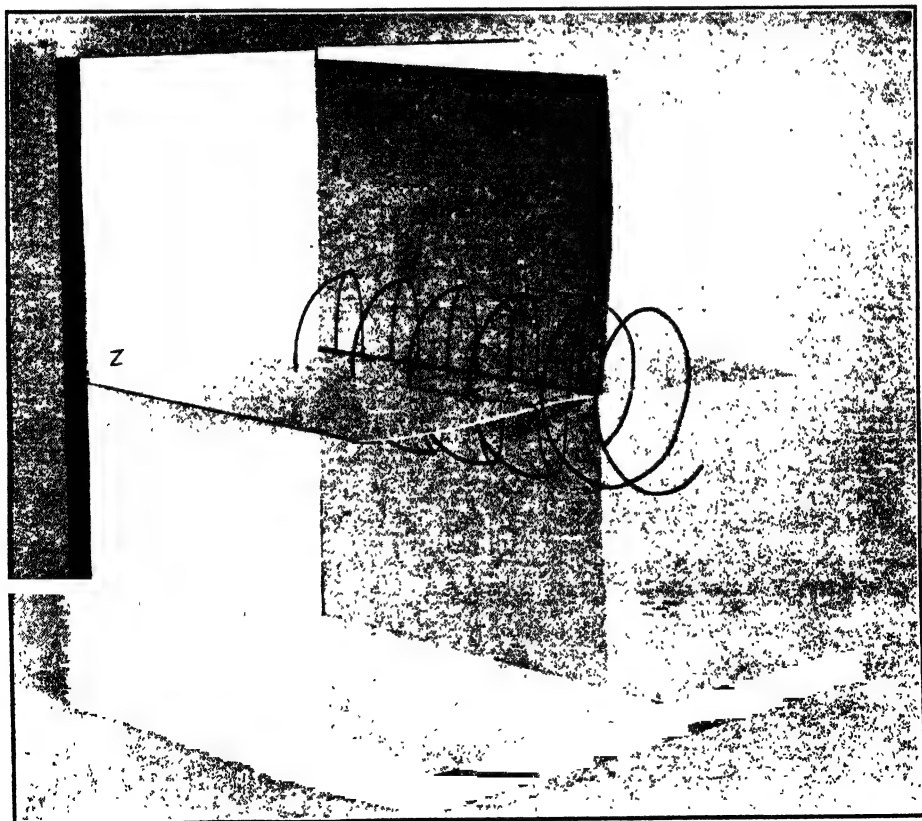


FIG. 5

circularly polarized light is *levo* since, to an observer stationed at *Y* with the light coming to his eye, the spiral proceeds in a counterclockwise direction. By making the phase difference 90° in the opposite direction *dextro* circularly polarized light is produced. If the phase difference is not 90° or if the amplitudes are unequal *elliptically polarized* light results.

Circularly polarized light is produced by passing plane-polarized light through a glass prism known as Fresnel's rhomb. This glass prism ($n_D = 1.504$) has its faces cut and polished so that the acute angle (*A*) is 54° .

A cross section of such a prism is shown in Fig. 6.

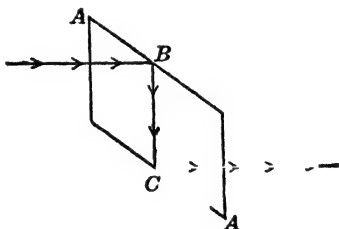


FIG. 6

A beam of light normal to the face will be totally reflected at *B* and again at *C*. At each reflection with the angle of incidence equal to 54° and an index of refraction of 1.504, a phase difference of one-eighth of a period is introduced between the vibrations in and at right angles to the plane of incidence. Hence, if the incident light is plane polarized at an angle of 45° to the plane of incidence (which is the plane of the paper in Fig. 6), a total phase difference of one-fourth of a period (90°) is introduced and the emergent light is *circularly polarized*. If the phase difference is not 90° or if the amplitudes of the two components are different the resultant light will be elliptically polarized.

A second method of producing circularly polarized light consists in passing monochromatic plane-polarized light through a thin crystalline plate which is doubly refracting. Very thin sheets of mica or selenite may be used or polished plates of quartz. These thin plates resolve the incident vibrations into two components at right angles to each other (*cf.* Fig. 4) which traverse the plate with different velocities and emerge with a phase difference dependent on the thickness of the plate. The thickness of the plate should be such as to retard one of the waves 90° or a quarter of a wavelength in order that the emergent light should be circularly polarized. It is evident that the wavelength of the light used determines the thickness of the plate.

Studies with Circularly Polarized Light. In attempting to secure more precise information concerning the effects which asymmetric

molecules exert upon light it has been found desirable to study the effects of circularly polarized light and elliptically polarized light. A correlation of the studies on rotatory dispersion (p. 268) and the absorption spectra has shown that *abnormal rotatory dispersions* are observed in the immediate vicinity of the specific absorption bands. Moreover, it was found that the beam of light emerging from an optically active substance was not plane polarized but elliptically polarized, provided that the wavelength of the light used was within certain of the absorption bands. Next, the absorption of *dextro-* or *levo-circularly polarized* light was studied, and it was found that the absorption by an optically active molecule is dependent on the wavelength of the circularly polarized light. If the circularly polarized light possessed a wavelength in the neighborhood of the characteristic absorption bands of groups concerned with the optical activity of the molecule, then the beams of *dextro-* and *levo-circularly* polarized light were absorbed to a different extent. At all other wavelengths the coefficients of absorption were equal. This phenomenon is known as *circular dichroism* or the "Cotton effect," since Cotton in 1896 demonstrated that alkaline solutions of copper *d*-tartrate and *l*-tartrate absorbed *dextro-* and *levo-circularly* polarized light to different extents.

The differences which *d*- and *l*-asymmetric molecules exhibit toward *d*- and *l*-circularly polarized light has been used as a basis for an explanation of the mechanism by which optically active substances rotate the plane of polarized light. According to Fresnel, the beam of plane-polarized light is split into two circularly polarized beams of light with opposite rotations. If the compound is optically inactive these two spirals travel with the same velocity and upon emerging recombine with a resultant which is plane-polarized light.

Thus, in Fig. 7, the dotted circle represents the projection of the two circularly polarized components on the *XZ*-planes, the beams of light traveling perpendicular to the paper. At the end of a certain time, the right circularly polarized light reaches the point P_D , and the *levo* beam of light reaches the point P_L . If the two beams travel at the same rate, then the arc $RP_D = RP_L$ and the resultant beam is the plane-polarized component along *OX*. It is evident that all the resultants will lie on the axis *XOX'* as long as the velocities of the *d*- and *l*-circularly polarized beams are equal.

If, however, the plane-polarized light passes through an *optically active* compound then the *velocities* of the *d*- and *l*-circularly polarized light are different. Suppose that the *d*-circularly polarized light travels faster than the *l*-beam; then, as shown in Fig. 8, after a certain time the *d*-ray will have reached the point P_D , and the *l*-beam will travel only as far as

P_L . The resultant of these two circularly polarized beams is found by completing the parallelogram of forces, and the resultant is OQ , which represents the plane in which the polarized light is now vibrating. It is evident that the plane of vibration of the emerging light differs by the angle θ from the plane of the incident light. Fresnel confirmed experimentally the correctness of his explanation by means of a triple quartz

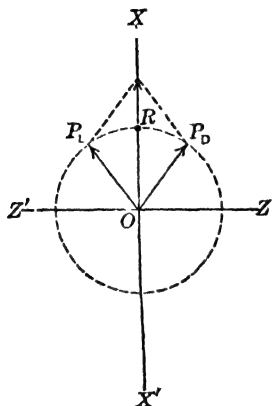


FIG. 7

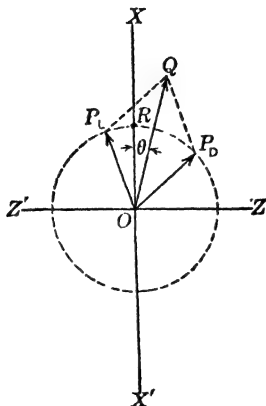


FIG. 8

prism. Cornu and von Lang later confirmed it using a single quartz prism and finally Fleischl established this explanation for optically active solutions.

Exactly how the optically active molecule resolves the plane-polarized light into these two circularly polarized beams and why it slows down one of them is not definitely established. It is known that only the valence electrons have any effect on light, and apparently the unsymmetrical distribution of the positive charges in an asymmetric molecule induces electronic vibrations which exhibit the selective action on the vector directions of the light photons constituting the *d*- and *l*-circularly polarized light.

A study of the absorptive powers of various groups for *d*- and *l*-circularly polarized light has shown that those groups having absorption bands nearest the visible are the most effective in causing a high specific rotation. Hence, if only one group attached to the asymmetric carbon atom absorbs circularly polarized light near the visible region, the stereochemical position of this group will determine the direction in which the plane of polarized light is rotated. If more than one group has absorption bands near the visible, then it is necessary to calculate the effect of each group. A study of these phenomena appears to offer a means of independently correlating the configurations of related compounds and thus of establishing whether or not a Walden inversion takes place.

The relationships which have been developed between the various factors have been summarized by Landolt in 1906 and more recently by Lowry (1935), whose excellent monograph should be consulted. References to the work of the investigators mentioned above will be found in the books cited below.

GENERAL REFERENCES

WOOD, "Physical Optics," Macmillan, New York (1934).

LANDOLT, "The Optical Rotating Power," translated by LONG, Chem. Pub. Co., Easton, Pennsylvania (1902).

LOWRY, "Optical Rotatory Power," Longmans, Green and Co., London (1935).

RITCHIE, "Asymmetric Synthesis and Asymmetric Induction," Oxford University Press, London (1933).

Factors Influencing Optical Rotation

Examination of formulas (1) and (2), developed by Biot for calculating the specific rotation of optically active compounds, shows that certain

(1) *Pure Compounds*

$$[\alpha]_{\lambda}^T = \frac{a}{l \cdot d}$$

(2) *Solutions*

$$[\alpha]_{\lambda}^T = \frac{100a}{l \cdot g \cdot d} \quad \frac{100a}{l \cdot c}$$

conditions must be established experimentally. Hence, it is evident that the magnitude and direction of the specific rotation are dependent upon and vary with temperature, wavelength of the light, concentration, and nature of the solvent, since these factors appear in the above equations. Extensive investigations have been carried out in order to analyze the results obtained by variations in these factors. Landolt³ in 1902, and Lowry⁴ in 1935, summarized the data which had been accumulated, and these books contain complete information on this subject. In the following discussion, a few specific examples have been chosen from a large mass of data in order to illustrate the effect of variations in the factors mentioned above.

Temperature. The specific rotation of a compound may either increase or decrease with a rise in temperature. For example, Krecke⁵ found that the specific rotation of *d*-tartaric acid increased with a rise in temperature (Table I).

³ Landolt, "The Optical Rotating Power," translated by Long, Chem. Pub. Co. Easton, Pennsylvania (1902).

⁴ Lowry, "Optical Rotatory Power," Longmans, Green and Co., London (1935).

⁵ Krecke, *Arch. néerland.*, **7**, 97 (1872).

TABLE I

| TEMPERATURE | TARTARIC ACID CONCENTRATION OF AQUEOUS SOLUTIONS | | |
|-------------|---|-------|-------|
| | 10% | 20% | 40% |
| 0° | 9.95° | 8.66° | 5.45° |
| 100 | 23.79 | 21.48 | 17.50 |

On the other hand, Gernez ⁶ observed a slight decrease in the rotation of turpentine (impure *l*-pinene) as the temperature was increased (Table II).

TABLE II

| TEMPERATURE | M_D (TURPENTINE) |
|-------------|--------------------|
| 11° | -36.53° |
| 98 | -36.04 |
| 154 | -35.81 |
| 168 (vapor) | -35.49 |

Pictet ⁷ found that the specific rotation of methyl *d*-tartrate increased from +2.14° at 20° C. to +6.00° at 100° C., whereas Cook ⁸ showed that the direction of rotation of aspartic acid could be inverted by a rise in temperature (Table III).

TABLE III

| TEMPERATURE | $[\alpha]_D^{20}$ (ASPARTIC ACID) |
|-------------|-----------------------------------|
| 20° | +4.36° |
| 75 | 0.00 |
| 90 | -1.86 |

A similar inversion in the specific rotation of malic acid ⁹ occurs at certain concentrations as the temperature is increased.

No general statements can be made relating the specific rotation with temperature change. Each compound must be studied, and the change in rotation with temperature expressed graphically or by an equation which is limited in its application to that particular substance. The temperature effect is intimately connected with the phenomena of dissociation, association, and solvation which are discussed later.

Wavelength of Light. In 1853 Biot pointed out that the magnitude of the rotation of plane-polarized light depended on the wavelength of the light, and was approximately inversely proportional to the square of

⁶ Gernez, *Compt. rend.*, **58**, 1108 (1864).

⁷ Pictet, *Arch. Genève*, [3] **7**, 82 (1882).

⁸ Cook, *Ber.*, **30**, 294 (1897).

⁹ Thomsen, *Ber.*, **15**, 441 (1882).

the wavelength. This change of rotation with change of wavelength of the light was called *rotatory dispersion*. If this dispersion follows the simple equation:

$$[\alpha]^T = \frac{A_0}{\lambda^2 - \lambda_0^2}$$

where $[\alpha]^T$ = specific rotation, A_0 = constant for compound, λ and λ_0 = characteristic wavelengths, then $[\alpha]$ increases regularly with decreasing values of λ over the portion of the spectrum considered, the dispersion curve is an hyperbola, and the rotatory dispersion is said to be *normal*. If the dispersion does not follow this simple equation, but requires a complex expression of the type

$$[\alpha]^T = \frac{A_0}{\lambda^2 - \lambda_0^2} + \frac{A_1}{\lambda^2 - \lambda_0^2} + \cdots = \sum \frac{A}{\lambda^2 - \lambda_0^2}$$

then the dispersion is *abnormal* or *complex*.

The study of the absorption of light by organic compounds has led to the discovery of the fact that compounds possess characteristic absorption bands. Such absorption spectra (p. 1774) have been correlated with the structure of the molecule, and it has been fairly well established that each of the bands is intimately dependent upon the presence of definite groups in the molecule. In an optically active compound, certain of these bands seem to be directly connected with the groups concerned with optical rotatory power of the molecule. Hence, the specific rotation of a compound changes markedly if the measurements are made with light of a wavelength which corresponds to one of these absorption bands. As a specific example, the results obtained by W. Kuhn and Gore¹⁰ on a solution of *d*-camphor in hexane are shown in Fig. 9.

The molecular rotation curve, *A*, undergoes abrupt changes as the region represented by the absorption curve, *B*, is approached and passed. At wavelengths of light remote from the absorption curve, very little change occurs in the optical rotation as the wavelength is changed.

If the absorption bands occur in the visible range, as with colored compounds, difficulty is often experienced in determining the optical rotation. It is then necessary to determine the specific rotation at different wavelengths. With colorless compounds, satisfactory results are obtained by using a monochromatic source of light—usually the sodium D line. The wavelength of the light used must always be specified. The importance of this factor has been emphasized by Karrer during a study of the configurational relationships between the naturally occurring α -amino acids, α -halogen acids, and α -hydroxy acids. Table

¹⁰ Kuhn and Gore, *Z. physik. Chem.*, **12B**, 392 (1931).

IV contains some of the rotatory dispersion data obtained by Karrer and Kaase,¹¹ which demonstrate the wide variation in rotation by change in wavelength of light and, in one instance, the change in the rotation of a compound from *levo* to *dextro*.

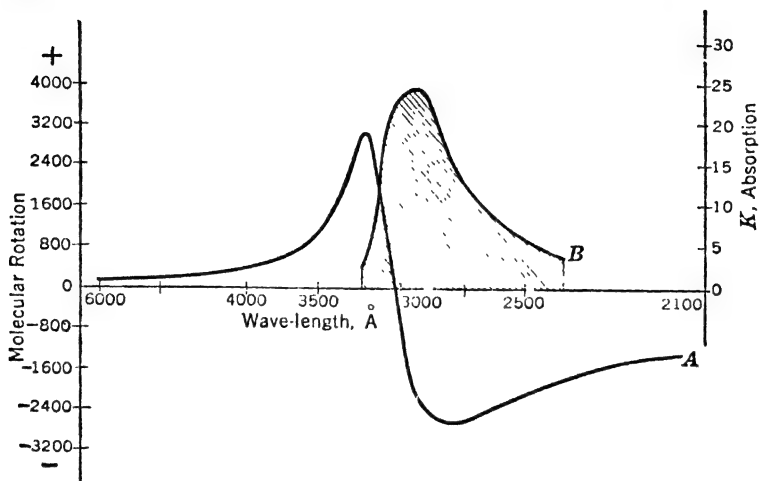


FIG. 9. Rotatory Dispersion of *d*-Camphor in Hexane.

A = molecular rotation; B = absorption.

Solutions. The specific rotatory power of an optically active solute dissolved in a solvent is dependent upon the following factors:

1. Nature of solute.
2. Nature of solvent.
3. Concentration.
4. Dissociation.
5. Association.

All these factors are interdependent and must be considered together in discussing the specific rotation of any particular solution of a compound.

In 1873, Landolt¹² studied the rotations of the lithium, sodium, potassium, and ammonium salts of *d*-tartaric acid and found that the molecular rotations of these salts approached the same value as the solution was made more and more dilute. A few years later, 1876, Oudemans¹³ found that dilute solutions of salts of quinine with different acids gave constant molecular rotations. Hädrich,¹⁴ in 1893, also studied the effect of dilution and pointed out the relationship between the optical rotatory power of ionogens with the electrolytic dissociation

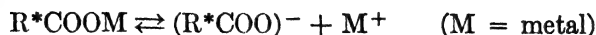
¹¹ Karrer and Kaase, *Helv. Chim. Acta*, **2**, 436 (1919).

¹² Landolt, *Ber.*, **6**, 1077 (1873).

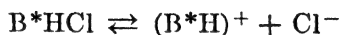
¹³ Oudemans, *Ann.*, **182**, 52 (1876).

¹⁴ Hädrich, *Z. physik. Chem.*, **12**, 476 (1893).

theory of Arrhenius which had been proposed in the meantime (1887). Thus, a dilute solution of a salt of an optically active acid owes its rotation entirely to the optically active anion, whereas, in more concen-

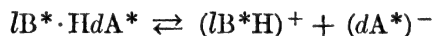


trated solutions, both the undissociated salt and the anion affect the plane of polarized light. Similarly, the dissociation of a salt of an optically active base (B^*)



produces the optically active cation, and when dissociation is complete, only the cation is optically active and the anion is without appreciable effect.

The molecular rotation of a salt of an optically active base with an optically active acid also reaches a constant value in dilute solutions, and this value is the algebraic sum of the rotations of the cation plus anion. For example, the dissociation of such a salt takes place as follows:



In dilute solution, $M_D = M_D \text{ cation} + M_D \text{ anion}$.

As a specific example, the average value of the molecular rotation of morphine α -bromocamphor- π -sulfonate in dilute aqueous solution was found to be equal to -100° . Dilute aqueous solutions of morphine hydrochloride gave an average value of -371° for the morphine cation and dilute aqueous solutions of α -bromocamphor- π -sulfonic acid gave an average molecular rotation of $+271^\circ$ for the anion. Hence, the rotation of the salt should be $-371^\circ + 271^\circ = -100^\circ$, which checks the actual observed value.

From the above discussion it is evident that the specific rotation of a solute, which is capable of ionization when dissolved in an ionizing solvent, is dependent upon the degree of dissociation, which in turn varies with the concentration and, it may also be added, with the temperature.

The factor of association of molecules of the solute also influences the specific rotation although the data on this point are rather meager. Different specific rotations are observed for an optically active liquid depending on whether the rotation is determined on the pure liquid, on a solution of the liquid, or on the vapor of the compound. For example, the $[\alpha]_D^{20}$ for pure methyl *d*-tartrate¹⁵ was found to be $+2.1^\circ$, whereas a benzene solution gave a value of -8.8° . Cryoscopic determinations showed a molecular weight of 411 in benzene, whereas the calculated value is 178.

¹⁵ Freundler, *Ann. chim. phys.*, [7] **4**, 256 (1895).

Structure. The attempts which have been made to correlate the degree of optical activity with the structure of the molecule have not led to the discovery of any definite relationships. A study of the *l*-menthyl esters of monosubstituted acetic acids has shown that there is no regularity in the change of molecular rotation with change in polarity of the substituents.¹⁶ Some of the data are given in Table V.

TABLE V
l-MENTHYL ESTERS OF SUBSTITUTED ACETIC ACIDS

| $\text{XCH}_2\text{CO}_2\text{C}_{10}\text{H}_{19}(\text{l})$ | | | |
|---|---------------------------------------|---------------------------|---|
| $\text{X} =$ | Dipole Moment $\mu \times 10^{18}$ | k of acid | <i>l</i> -Menthyl Ester $[\text{M}]_{\text{D}}^{20}$ |
| $\text{N}(\text{CH}_3)_2$ | +1.4 | 1.3×10^{-10} (?) | -156.9 |
| H | — | 1.8×10^{-5} | -157.3 |
| CH_3 | +0.4 | 1.4×10^{-5} | -160.2 |
| CO_2H | -0.9 | 160×10^{-5} | -160.2 |
| OC_2H_5 | — | 23×10^{-5} | -160.6 |
| OCH_3 | -1.2 | 33×10^{-5} | -165 |
| OH | -1.7 | 15×10^{-5} | -165 (at 94° C) |
| Br | -1.5 | 138×10^{-5} | -169 |
| Cl | -1.5 | 155×10^{-5} | -171 |
| CN | -3.8 | 370×10^{-5} | -174 |

When the polar group is in closer proximity to the asymmetric center than in the compounds just described, the variation of molecular rotation is greater. A series of products formed by the condensation of aromatic aldehydes with *d*-phenyl oxynaphthyl methylamine showed in general a decrease of molecular rotation with increase of the ionization constants of the acids corresponding to the aldehydes.

The molecular rotations of several homologous series of compounds have been determined. Pickard and Kenyon¹⁷ prepared the series of alcohols shown in Table VI and the series of esters shown in Table VII.

TABLE VI
 $[\text{M}]_{\text{D}}^{20}$ OF $\text{CH}_3\text{CHOHR}(n)$ AND $\text{C}_2\text{H}_5\text{CHOHR}(n)$

| $[\text{M}]_{\text{D}}^{20}$ | $[\text{M}]_{\text{D}}^{20}$ |
|---|--|
| Methylethylcarbinol 10.30 | Ethyl- <i>n</i> -propylcarbinol 2.01 |
| Methyl- <i>n</i> -propylcarbinol 12.10 | Ethyl- <i>n</i> -butylcarbinol 9.43 |
| Methyl- <i>n</i> -butylcarbinol 11.80 | Ethyl- <i>n</i> -amylcarbinol 10.69 |
| Methyl- <i>n</i> -amylcarbinol 12.00 | Ethyl- <i>n</i> -hexylcarbinol 10.63 |
| Methyl- <i>n</i> -hexylcarbinol 12.70 | Ethyl- <i>n</i> -heptylcarbinol 10.58 |
| Methyl- <i>n</i> -heptylcarbinol 12.90 | Ethyl- <i>n</i> -octylcarbinol 10.74 |
| Methyl- <i>n</i> -octylcarbinol 13.70 | Ethyl- <i>n</i> -nonylcarbinol 11.09 |
| Methyl- <i>n</i> -nonylcarbinol 14.00 | Ethyl- <i>n</i> -decylcarbinol 12.44 |
| Methyl- <i>n</i> -decylcarbinol 14.50 | Ethyl- <i>n</i> -undecylcarbinol 12.56 |
| Methyl- <i>n</i> -undecylcarbinol 14.40 | |

¹⁶ Rule, *Trans. Faraday Soc.*, **26**, 325 (1930).

¹⁷ Pickard and Kenyon, *J. Chem. Soc.*, **99**, 49 (1911); **103**, 1923 (1911); **105**, 830 (1914)

TABLE VII
 $[M]_D^{20}$ OF COMPOUNDS OF THE FORMULA $\text{CH}_3\text{CH}(\text{OCOR})\text{R}'$

| (OCOR) | $\text{CH}_3\text{CH}(\text{OCOR})\text{C}_2\text{H}_5$ $[M]_D^{20}$ | $\text{CH}_3\text{CH}(\text{OCOR})\text{C}_3\text{H}_7(n)$ $[M]_D^{20}$ | $\text{CH}_3\text{CH}(\text{OCOR})\text{C}_4\text{H}_9(n)$ $[M]_D^{20}$ | $\text{CH}_3\text{CH}(\text{OCOR})\text{C}_6\text{H}_{11}(n)$ $[M]_D^{20}$ |
|-----------------|---|--|--|---|
| Acetate..... | 29.70 | 22.30 | 14.59 | 13.00 |
| Propionate..... | 31.00 | 23.66 | 15.43 | 14.40 |
| Butyrate..... | 31.63 | 24.92 | 18.62 | 18.91 |
| Valerate..... | 32.74 | 27.54 | 20.75 | 20.52 |
| Hexoate..... | 32.10 | | 21.68 | 21.34 |
| Heptoate..... | 32.31 | | 22.17 | 21.72 |
| Octoate..... | 32.28 | | 22.69 | 21.95 |
| Nonoate..... | 32.17 | | 22.55 | 22.26 |

The data on the alcohols (Table VI) indicate merely that the molecular rotation of the molecule gradually increases with the length of the alkyl group and that the increment becomes smaller. On the other hand, the molecular rotations of the optically active aliphatic esters (Table VII) appear to approach limiting values with increase in the length either of the acyl group or of the alkyl group.

It is obvious from such results as have been given that no deductions concerning the molecular rotation of a molecule can be drawn from a knowledge of its structure.

Concentration. The optical rotation of a compound in solution varies with the concentration, since the degree of dissociation or association is dependent on the concentration. Undoubtedly solvation also plays an important role, and this factor is related to concentration.

Solvent. The solvent itself also profoundly influences the rotation observed. Pribram¹⁸ determined the rotations of 5 per cent solutions of *d*-tartaric acid in a variety of solvents, some of the results being shown in Table VIII.

TABLE VIII
OPTICAL ROTATION OF *d*-TARTARIC ACID IN DIFFERENT SOLVENTS

| Solvent | $[\alpha]_D^{20}$ |
|---------------------------------|-------------------|
| Water | +14.40° |
| Ethanol | +3.79 |
| Ethanol + benzene (1 : 1) | -4.11 |
| Ethanol + toluene (1 : 1) | -6.19 |
| Ethanol + chlorobenzene (1 : 1) | -8.09 |

It is clear from the data in Table VIII, and also from numerous other studies, that the solvent influences not only the magnitude but also the direction of rotation. Hence, it is necessary to specify the solvent when speaking of a certain optical isomer as being the *d*-isomer or *l*-isomer.

It should be mentioned that no change in configuration is involved in the phenomena under discussion; i.e., it is exactly the same optical form which rotates polarized light to the *right* in one solvent, and to the *left* in another solvent; to the right at one concentration and to the left at another; to the right at one temperature and to the left at a different temperature.

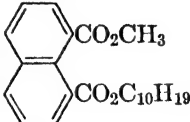
During the past ten years a systematic study of the relationship between the solvent and optical rotatory power of a compound has been undertaken by H. G. Rule and his co-workers¹⁹ in order to gain more

¹⁸ Pribram, *Ber.*, **22**, 6 (1889).

¹⁹ Rule and co-workers, *J. Chem. Soc.*, 674, 2652 (1931); 1400, 1409, 2332 (1932); 376, 1217 (1933); McLean, *ibid.*, 351 (1934).

precise information concerning the change in optical rotatory power caused by solvents. These investigations were carried out on compounds and solvents so chosen that the factors of ionization and association of solute molecules were excluded.

The optical rotation of methyl *l*-menthyl naphthalate in a large number of solvents was determined. It was found that the dipole moment of the solvent furnished a physical property which enabled correlations to be made, provided that the polar solvents were classified according to the parent hydrocarbon from which they were derived. The non-polar solvents constituted a separate class. Four series of solvents were obtained in which the optical rotation varied sympathetically with the dipole moment. Some of the data are shown in Table IX, the upper half of which represents the polar solvents which may be regarded as derived from methane.

TABLE IX
 VARIATION IN OPTICAL ROTATION OF  WITH THE DIPOLE
 MOMENTS OF THE SOLVENTS

| | | Solvent | Dipole Moment $\mu \times 10^{18}$ | $[M]_{5461}^{20}$ |
|-----------------------|---|---------------------------------|---------------------------------------|-------------------|
| Polar Solvents | { | CH ₃ NO ₂ | 3.8 | -219° |
| | | CH ₃ CN | 3.2 | -239 |
| | | CH ₃ CHO | 2.7 | -316 |
| | | CH ₃ I | 1.3 | -336 |
| | | CH ₃ OH (associated) | 1.6 | -383 |
| | | | | |
| Non-polar Solvents | { | CS ₂ | 0 | -437 |
| | | CCl ₄ | 0 | -563 |
| | | C ₆ H ₁₂ | 0 | -651 |
| | | C ₆ H ₁₄ | 0 | -653 |
| | | C ₇ H ₁₆ | 0 | -653 |

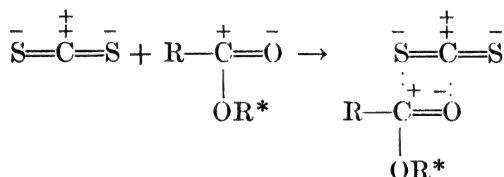
Examination of the data in Table IX shows that the molecular rotation *increases* as the dipole moment of the solvent *decreases*. Three similar series of solvents derived from ethane, benzene, and naphthalene were also studied. The results demonstrate that there is little or no regularity when solvents of one series are compared with those of another. Hence, the most favorable conditions for the observation of regularities are obtained when all the solvents are derived from the same parent hydrocarbon.

The solvents which have no dipole moment give the largest molecular

rotations. There is, however, a large variation in the solvents with no dipole moment. Such compounds fall into two classes.

(a) *Compounds with No Permanent Dipoles.* The paraffin hydrocarbons are examples of such molecules. Consideration of the data in Table IX shows that a maximum and constant molecular rotation of the ester is observed in pentane, hexane, and heptane. It seems reasonable to believe that in these solvents there is a minimum of association between solute and solvent.

(b) *Compounds with Neutralized Dipoles.* Carbon disulfide and carbon tetrachloride are molecules in which the electric moments are opposed to each other, and hence are non-polar with reference to a uniform external field. However, such a molecule may exert a definite force on a point charge or dipole in its immediate neighborhood. If the solute possesses a dipole, then association with the solvent may occur.



Such association would tend to decrease the rotatory power, since it would decrease the polarity of the solute. The magnitude of the rotation of a solute has been experimentally demonstrated to depend upon the polarity of the groups in the solute located near the asymmetric carbon atom. It is an association of this type which is advanced to explain the fact that methyl *l*-menthyl naphthalate possesses a molecular rotation of only -437° in carbon disulfide as a solvent, but a rotation of -653° in the paraffin hydrocarbons.

The extent of this association between solute and solvent will depend not only on the magnitude of the dipole moments of both, but also on the steric effects which influence the closeness of association of solvent and solute, and are dependent upon the individual structure of each. An illustration of the way in which steric effects may dominate the results to be expected from the dipole moments is demonstrated by using the isomeric butyl chlorides as solvents. The data for the rotation of methyl *l*-menthyl naphthalate are given in Table X.

tert-Butyl chloride has the *largest* dipole moment, and should produce the *lowest* rotation of the ester. However, it actually leads to the highest rotation because of the steric or screening effect of the three methyl groups on the carbon-chlorine dipole. The *n*-butyl chloride shows the minimum, and the isobutyl chloride an intermediate rotation of the

ester, since the former has the minimum and the latter an intermediate steric effect.

TABLE X

| Solvent | Dipole Moment $\mu \times 10^{18}$ | $[M]_{5461}^{20}$ |
|---|--|-------------------|
| $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$ | 1.90 | -450° |
| $\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3\text{CHCH}_2\text{Cl} \end{array}$ | 1.90 | -464 |
| $\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{C}-\text{Cl} \\ \\ \text{CH}_3 \end{array}$ | 2.14 | -511 |

Finally, Rule and his students have obtained results which indicate that the dipoles in substituted benzene derivatives may act independently in associating with the optically active solute. Table XI shows some of the data obtained on methyl *l*-menthyl naphthalate when dissolved in various aromatic compounds as solvents.

TABLE XI

| Solvents | Dipole Moment $\mu \times 10^{18}$ | $[M]_{5461}^{20}$ | $\Delta = [M]_{\text{Benzene}} - [M]_{\text{Solvent}}$ |
|---|--|-------------------|--|
| C_6H_6 | 0 | -543° | .. |
| $\text{C}_6\text{H}_5\text{Cl} + \text{C}_6\text{H}_6$ | 1 52 | -501 | 42° |
| <i>o</i> - $\text{C}_6\text{H}_4\text{Cl}_2 + \text{C}_6\text{H}_6$ | 2 25 | -470 | 73 |
| <i>p</i> - $\text{C}_6\text{H}_4\text{Cl}_2 + \text{C}_6\text{H}_6$ | 0 | -463 | 80 |
| $\text{C}_6\text{H}_5\text{NO}_2 + \text{C}_6\text{H}_6$ | 3 9 | -527 | 16 |
| <i>m</i> - $\text{C}_6\text{H}_4(\text{NO}_2)_2 + \text{C}_6\text{H}_6$ | 3.7 | -510 | 33 |
| <i>p</i> - $\text{C}_6\text{H}_4(\text{NO}_2)_2 + \text{C}_6\text{H}_6$ | 0 | -508 | 35 |

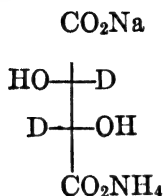
Careful examination of the data in Table XI shows that when the disubstituted benzenes are used as solvents the drop in rotation (Δ) of the ester is nearly double that observed when a monosubstituted benzene is used as the solvent in place of benzene.

In general, it now appears that association between solute and solvent is one of the important factors influencing optical rotatory power, and that the dipole moments or neutralized dipoles of the solvent are factors in determining the degree of association.

Recent investigations have shown that rotations of optically active compounds in hydrogen-containing solvents differ from those observed in the corresponding deuterium solvents. The magnitude of the change in specific rotation is not great (usually less than one degree). A review of these studies has been contributed by Buchanan.²⁰

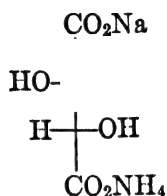
²⁰ Buchanan, *Chemistry & Industry*, 748 (1938).

Deutero Compounds. The replacement of hydrogen by deuterium in an optically active compound causes a slight change in the optical rotatory power. For example, Erlenmeyer and Bitterlin²¹ prepared the two compounds shown in Figs. 10 and 11 and found that the deutero compound had a slightly lower specific rotation in aqueous solution.



$$\alpha_D = 31.5^\circ$$

FIG. 10



$$\alpha_D = 32.8^\circ$$

FIG. 11

Molecules in which the sole cause of asymmetry is the replacement of hydrogen by deuterium have been studied in order to determine whether optical activity is possible. The structures shown in Fig. 12 are

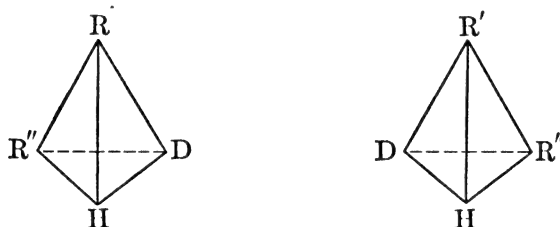


FIG. 12

certainly asymmetric according to definition, but the differences in optical rotatory power of the *d*- and *l*-forms may be exceedingly small. Up to the present time all compounds of this type have been found to be inactive or to have given such small observed rotations as to be indecisive.

Mention may be made of several ingenious attacks on this problem. Studies on α -pentadeuterophenylbenzylamine (Fig. 13) have shown that it could not be resolved,^{22, 23} contrary to earlier reports.²⁴ McGrew

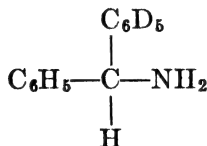


FIG. 13

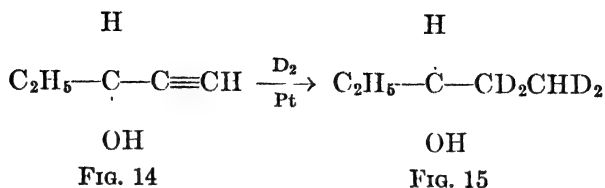
²¹ Erlenmeyer and Bitterlin, *Helv. Chim. Acta*, **23**, 207 (1940).

²² Adams and Tarbell, *J. Am. Chem. Soc.*, **60**, 1260 (1938).

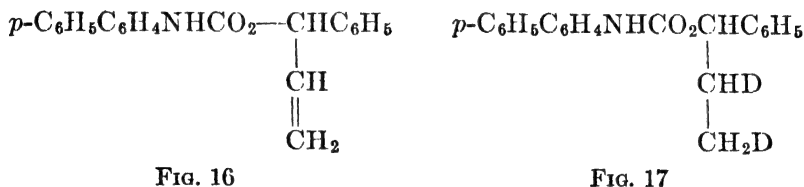
²³ Clemo, Raper, and Robson, *J. Chem. Soc.*, 431 (1939).

²⁴ Clemo and McQuillen, *ibid.*, 808 (1936).

and Adams²⁵ resolved 1-pentyn-3-ol (Fig. 14) and reduced it catalytically with deuterium to the tetradeutero compound of Fig. 15 which was found to be optically inactive.

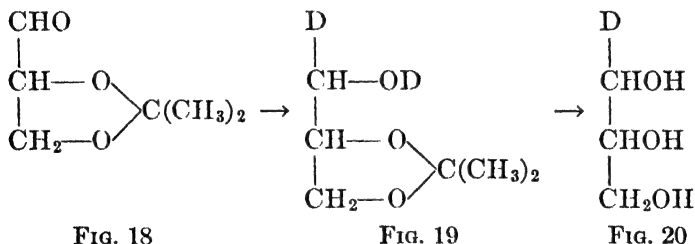


Coppock, Kenyon, and Partridge²⁶ prepared the *p*-phenylphenylurethan of *l*-phenylvinylcarbinol (Fig. 16) and reduced it with deuterium hoping to obtain diastereoisomers of Fig. 17, but no separation could be



effected. In another experiment the *l*-phenylvinylcarbinol was reduced with deuterium and the 3,5-dinitrobenzoate fractionally crystallized. Hydrolysis to the alcohol and oxidation produced an inactive ketone.

Reduction of isopropylidene-*d*-glyceraldehyde (Fig. 18) produced the optically active compound of Fig. 19 which upon hydrolysis produced an optically inactive deuteroglycerol²⁷ (Fig. 20).

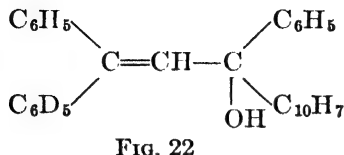
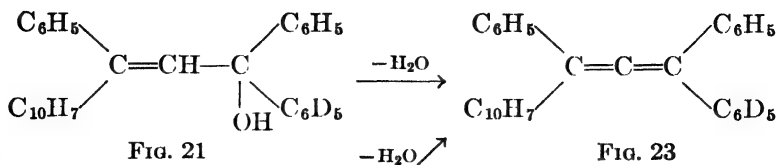


The two substituted allyl alcohols shown in Figs. 21 and 22 were dehydrated with *d*-camphor-10-sulfonic acid in an effort to obtain the optically active allene of Fig. 23, but the products showed no optical activity.²³

²⁵ McGrew and Adams, *J. Am. Chem. Soc.*, **59**, 1497 (1937).

²⁶ Coppock, Kenyon, and Partridge, *J. Chem. Soc.*, 1069 (1938).

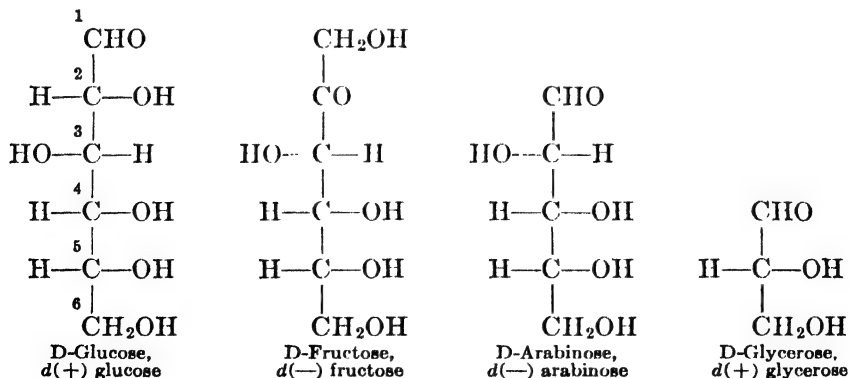
²⁷ Erlenmeyer, Fischer, and Baer, *Helv. Chim. Acta*, **20**, 1012 (1937).



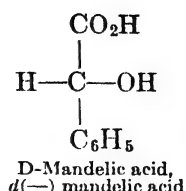
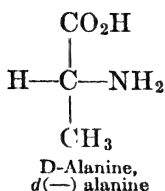
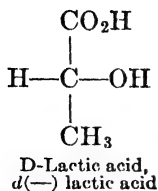
Configurational Notation

Notations have been introduced to indicate configurational relationships which are independent of the numerical value or sign of the specific rotation and denote the relative position which the groups about the asymmetric carbon atom possess.

According to one notation suggested by the Committee on Carbohydrate Nomenclature of the American Chemical Society, *dextro*-glycerose is chosen as the standard reference substance and denoted as D-glycerose and all compounds having the same configuration shall belong to the D-configurational series. Those having the opposite configuration shall belong to the L-series. Capital letters are used to denote configurations. When the Fischer projectional straight-chain formula of a compound belonging to the D-series is written vertically with carbon number one at the top, then the —OH (or other substituent such as OR, OAc, NH₂) of the terminal asymmetric carbon atom shall be placed to the right of the chain. If the formula is written horizontally it shall lie below the chain when carbon number one is to the right. A second notation uses the lower-case letters *d*- and *l*- to denote configuration, and plus (+) and minus (−) signs to show the rotation.* The following formulas illustrate these notations:



* Care must be exercised in using this notation, since many articles in the chemical literature use *d*- and *l*- indiscriminately for rotation or configuration. The Fischer convention is summarized by Hudson, *J. Chem. Ed.*, **18**, 353 (1941).



The mirror images of these compounds belong to the L-series, regardless of their rotations. The investigations of Clough,²⁸ Karrer,²⁹ Levene,³⁰ Freudenberg,³¹ and others have shown that all the α -amino acids obtained from proteins belong to the L-series, although the specific rotations of some of these are actually *dextro*.

Mutarotation

It has been observed experimentally that the rotatory power of a freshly prepared solution of certain optically active substances is not constant, but gradually changes, finally reaching a constant value (not zero) by reason of the establishment of an equilibrium. This change in rotatory power is termed *mutarotation*.^{*} Correlation of this phenomenon with the structure of the compounds which exhibit such behavior has shown that in each case a *configurational* or *structural* change has occurred.

Configurational Changes. Tanret³² found that two forms of D-glucose could be obtained. Freshly prepared solutions of one form, α -glucose, possessed a rotation of $+110^\circ$, and the second form, β -glucose, a rotation of $+17.5^\circ$. On standing, the rotations of both solutions changed and finally reached a constant value of $+52.5^\circ$. The essential changes involved, without consideration of the mechanism, are due primarily to an equilibrium between the forms shown in Figs. 24 and 25.

The proof of these structures is given in the chapter on carbohydrates (p. 1555), but the point to be noted here is that the mutarotation is caused by a change in the configuration of the groups attached to carbon atom number one (marked *). In general, it has been found that all reducing sugars and many of their derivatives exhibit mutarotation.]

The alkaloidal salts of certain substituted biphenyls exhibit mutarotation, which is due to the conversion of one form of the salt into an equi-

²⁸ Clough, *J. Chem. Soc.*, **113**, 526 (1918).

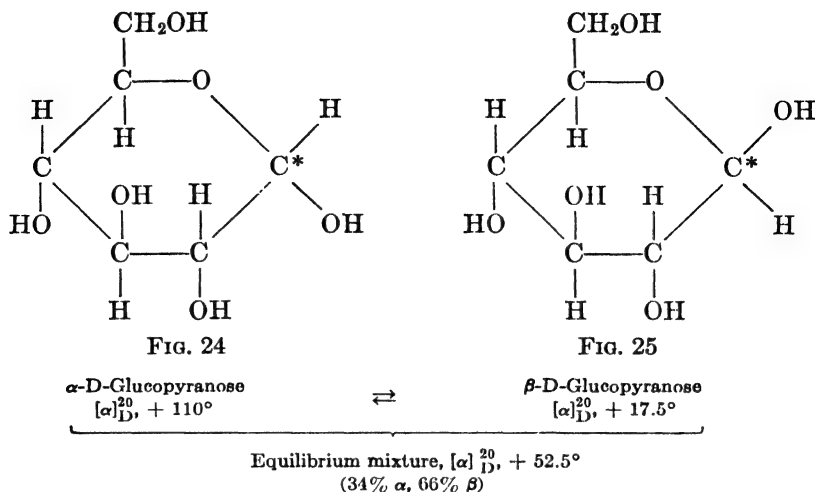
²⁹ Karrer, *Helv. Chim. Acta*, **6**, 957 (1923).

³⁰ Levene, see Gilman, "Organic Chemistry," John Wiley & Sons, New York (1938). First Edition, Vol. II, Chapter 21.

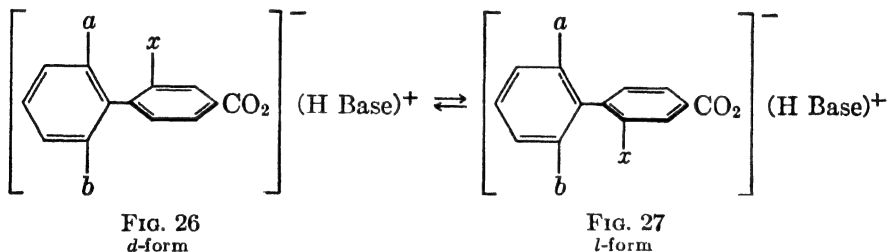
³¹ Freudenberg and co-workers, *Ber.*, **56**, 193 (1923); **57**, 1547 (1924); **58**, 1753 (1925) **60**, 2447 (1927); **61**, 1083 (1928).

* The terms multirotation and birotation have also been used.

³² Tanret, *Compt. rend.*, **120**, 1060 (1895).



librium mixture of this salt with its diastereoisomer. This is illustrated by Figs. 26 and 27.



The change in rotation results from the turning of one phenyl group through 180° about the pivot bond. It occurs in biphenyls whose *ortho* groups are small (see Part VIII). This represents a configurational change in the biphenyl part of the molecule; the alkaloidal part is unaffected.

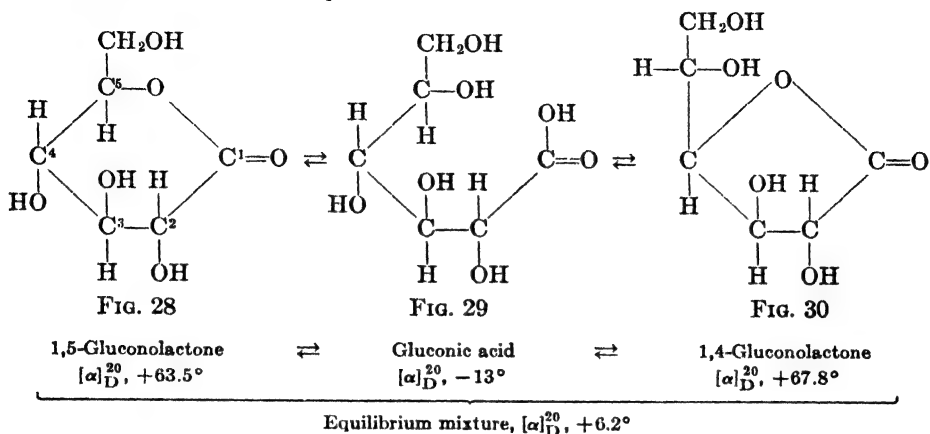
A spontaneous change in configuration at one center of asymmetry (with no changes at any other centers of asymmetry) leads to mutarotation and formation of an equilibrium mixture of two diastereoisomers, which are usually (but not necessarily) present in unequal amounts.

Structural Changes. Aqueous solutions of the lactones of certain of the sugar acids also mutarotate. Figures 28, 29, and 30 show the equilibrium between the lactones of gluconic acid.³³

The mutarotation is due to a structural change which results from the opening of the γ - (Fig. 30) or δ - (Fig. 28) lactone rings by hydrolysis to gluconic acid (Fig. 29). The groups attached to the asymmetric carbon

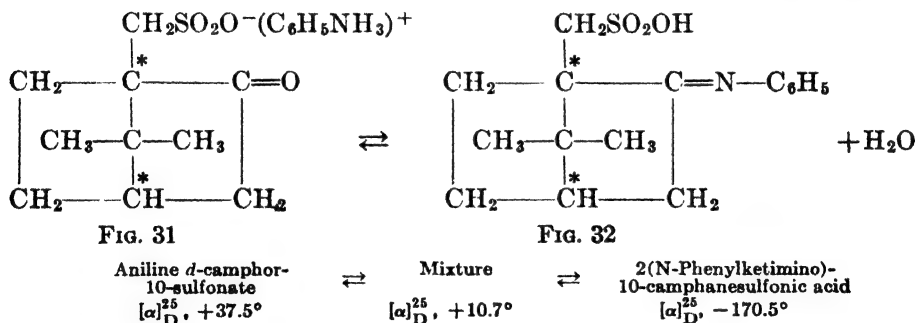
³³ Nef, *Ann.*, **403**, 204 (1914); Haworth and others, *J. Chem. Soc.*, **89**, 1899 (1926); **90**, 1237, 2436 (1927).

atoms, numbered 2, 3, 4, and 5, in each of the three molecules are different, and hence the optical rotatory power changes as one of the three molecules is converted into the equilibrium mixture. No configurational shift occurs about the asymmetric carbon atoms.



Another example in which a reaction causes mutarotation is found in the primary amine salts of *d*-camphor-10-sulfonic acid.³⁴ In anhydrous solvents an equilibrium is set up between the salt, ketimine, and water, as shown by Figs. 31 and 32.

The salt \rightleftharpoons ketimine reaction modifies the groups about the asymmetric carbon atoms (*), but no configurational change is involved. The possibility of such a transformation must be kept in mind when *d*-camphor-10-sulfonic acid is used as a resolving agent.



Mutarotation, due to structural change, is associated with molecules in which the groups about the asymmetric center are readily modified by the solvent or by some reaction which takes place easily in solution.)

(The rate of mutarotation, whether due to configurational or structural changes, is dependent upon temperature, solvent, and catalysts. All examples of mutarotation that are known take place in solution.)

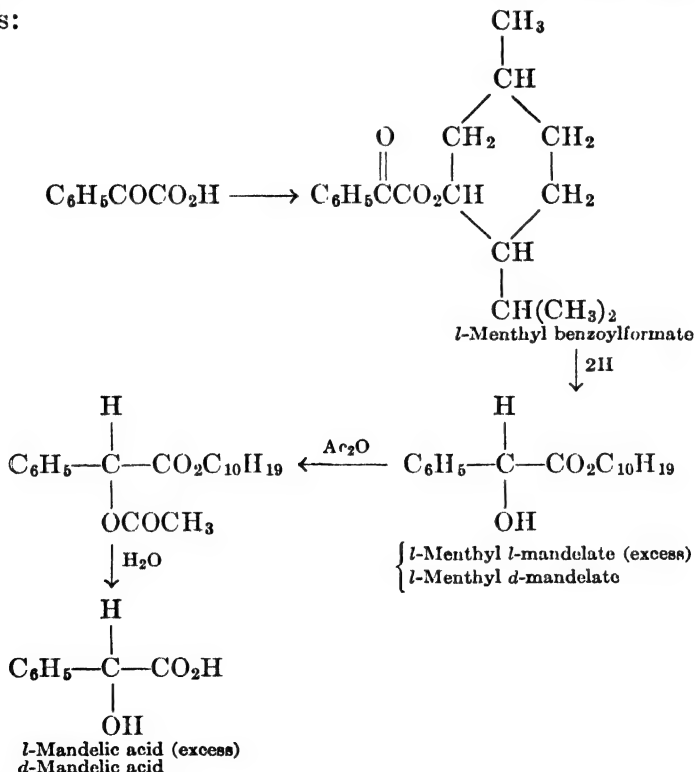
³⁴ Schreiber and Shriner, *J. Am. Chem. Soc.*, **57**, 1306, 1445, 1896 (1935).

Asymmetric Synthesis

The laboratory synthesis of asymmetric molecules, using ordinary chemical reactions and conditions, invariably produces the racemic modifications. On the other hand, most of the asymmetric molecules occurring in plants and animals are found as either the *dextro* or *levo* isomer. The problem of synthesizing optically active molecules, without recourse to resolution methods, has consequently intrigued organic chemists.

Emil Fischer,³⁵ in 1894, discussed this problem, and Marckwald,³⁶ in 1904, outlined in more precise terms the synthesis of optically active compounds. Marckwald defined "asymmetric syntheses" as those processes which produce optically active compounds from symmetrically constituted molecules by the intermediate use of optically active reagents, but without the use of any of the methods of resolution. This is the ordinary interpretation of the term "asymmetric synthesis" as employed today.

Many examples of asymmetric syntheses are known. An optically active mandelic acid was obtained by McKenzie³⁷ by the following series of reactions:



³⁵ Fischer, *Ber.*, **27**, 3231 (1894).

³⁶ Marckwald, *Ber.*, **37**, 349 (1904).

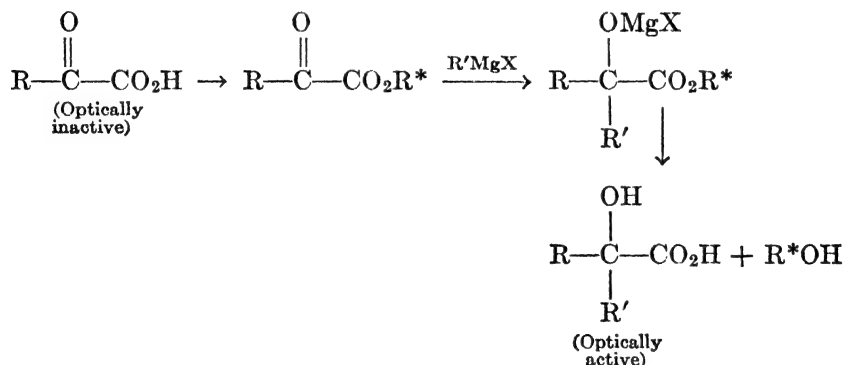
³⁷ McKenzie, *J. Chem. Soc.*, **85**, 1249 (1904); McKenzie and Humphries, *ibid.*, **95**, 1105 (1909).

The reduction of the *l*-menthyl ester of benzoylformic acid produces the two diastereoisomeric esters of mandelic acid in unequal amounts, and acetylation and hydrolysis result in a mandelic acid which contains an excess of the *levo* form. Thus, benzoylformic acid, which has no asymmetry and contains no asymmetric carbon atoms, is converted into mandelic acid, which does have an asymmetric carbon atom and is optically active. The nascent hydrogen may add to the ketone carbonyl group in two ways and at different rates because of the asymmetry of the molecule due to the presence of the *l*-menthyl group. In a similar manner, the pyruvates of *l*-menthol, *l*-borneol, and *l*-amyl alcohol yield optically active lactic acids³⁸ by reduction and hydrolysis.



where R^* is an optically active group.

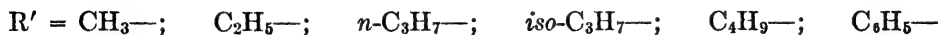
Treatment of optically active esters of α -ketonic acids with the Grignard reagent, followed by hydrolysis, also produces optically active hydroxy acids. The general reactions are as follows:



McKenzie and his co-workers³⁹ investigated some thirty examples of the above type, in which a variety of groups was used. Some of the groups were:



(Opt. act.) $R^* = l$ -menthyl; l -bornyl; d - and l -2-octyl

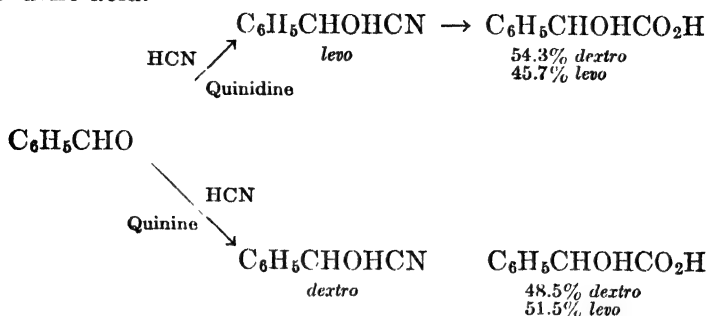


In each case, asymmetric syntheses are effected, and the resulting hydroxy acids contain an excess of one of the optical isomers.

³⁸ McKenzie, *ibid.*, **87**, 1373 (1905); McKenzie and Wren, *ibid.*, **89**, 688 (1906). McKenzie and Müller, *ibid.*, **95**, 544 (1909).

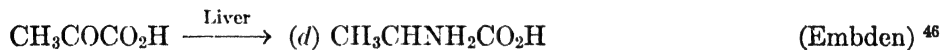
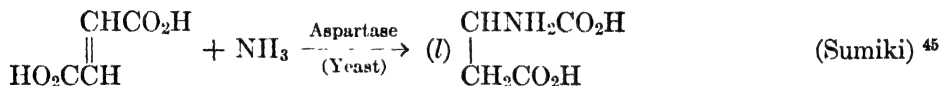
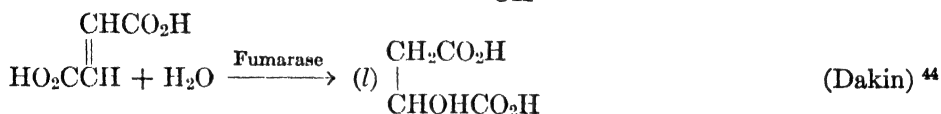
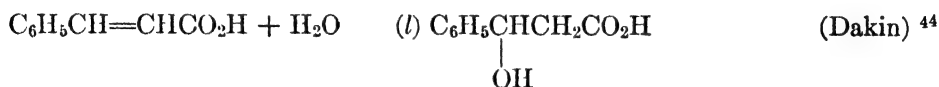
³⁹ McKenzie and co-workers, *ibid.*, **85**, 1249 (1904); **95**, 544 (1909); *Biochem. Z.*, **237** 1 (1931); **250**, 376 (1932); **231**, 412 (1931).

delic acid. In the presence of *l*-quinine, the same reactions produced a *levo* mandelic acid.



Five other aldehydes were shown to behave similarly, and the results parallel in a striking manner the asymmetric synthesis of optically active cyanohydrins from aldehydes and hydrogen cyanide in the presence of the enzyme, emulsin,⁴³ from almonds. Thus, *d*-mandelonitrile is obtained from benzaldehyde and hydrogen cyanide in large excess over *l*-mandelonitrile, since hydrolysis gives *l*-mandelic acid, which is optically pure after only two crystallizations.

Many additional asymmetric syntheses have been effected by enzymes. Some of these are listed below in order to give an idea of the scope of the studies.



⁴³ Rosenthaler, *ibid.*, **14**, 238 (1908); **17**, 257 (1909); **19**, 186 (1909); **26**, 1, 7 (1910); *Fermentforschung*, **5**, 334 (1921); *Arch. Pharm.*, **249**, 510 (1911).

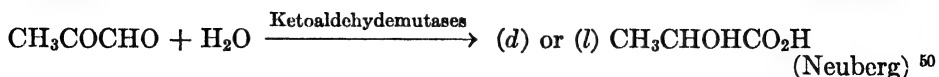
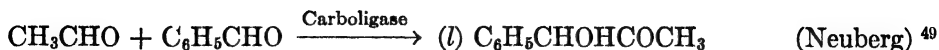
⁴⁴ Dakin, *J. Biol. Chem.*, **52**, 183 (1922).

⁴⁵ Sumiki, *Bull. Jap. Soc. Ferment.*, **23**, 33 (1928).

⁴⁶ Embden and Schmitz, *Biochem. Z.*, **29**, 423 (1910); **38**, 393 (1912).

⁴⁷ Neuberg and Lewite, *ibid.*, **91**, 257 (1918); Neuberg and Nord, *Ber.*, **52**, 2237, 2248 (1919).

⁴⁸ Rosenthaler, *Z. Untersuch. Nahr. u. Genussm.*, **20**, 448 (1910).



A comparison of the optical purity of the products of these enzymatic asymmetric syntheses with the previously cited asymmetric syntheses, using optically active reagents of known structure, shows that in the enzymatic reactions one optical antipode is often produced in great excess over its isomer and sometimes approaches 100 per cent optical purity.

Enzymes are complex organic compounds which are known to be optically active. The asymmetric synthesis effected by means of enzymes probably involves a combination of the substrate with the enzyme to produce an asymmetric molecule, which then undergoes selective hydration, reduction, or amination. Since the reaction is so one-sided, however, it is not certain that exactly the same mechanism is involved in enzymatic asymmetric syntheses as in the simple reactions studied by Marckwald and McKenzie.

The asymmetric syntheses brought about by enzymes are important because they offer a possible explanation for the continual production of optically active compounds in plants and animals. It should be noted, however, that none of these asymmetric syntheses offers an explanation of the origin of optically active compounds. The original optically active compound or enzyme necessary for these asymmetric syntheses is still to be accounted for.

Considerable interest has been manifested in a phenomenon termed *asymmetric induction*, which has been defined by Kortüm⁵¹ as the action of a force, arising in an optically active molecule, which influences adjacent symmetrical molecules in such a way that they become asymmetric. Two types are generally distinguished, intramolecular and intermolecular, depending on whether the systems involved are in the same or different molecules. At the present time, the evidence supporting the idea of asymmetric induction is not at all conclusive. An excellent review of the subject has been contributed by Ritchie.⁵²

An *absolute asymmetric synthesis* would consist in the preparation of an optically active molecule without using at any stage of the synthesis an

⁴⁹ Neuberg and Hirsch, *Biochem. Z.*, **115**, 282 (1921); Neuberg and Ohle, *ibid.*, **128**, 610 (1922).

⁵⁰ Neuberg, *ibid.*, **49**, 502 (1913); **51**, 484 (1913).

⁵¹ Kortüm, *Samml. chem. chem.-tech. Vorträge*, **10** (1932).

⁵² Ritchie, "Asymmetric Synthesis and Asymmetric Induction," Oxford University Press, London (1933).

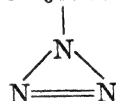
optically active reagent, and without using any of the methods of resolution. In order to induce the formation of an excess of one enantiomorph, the effect of various physical agents on the reactants has been studied. The only agent which has yielded interesting results is circularly polarized light (p. 285).

Cotton⁵³ attempted to effect an asymmetric decomposition by irradiating the alkaline copper *dl*-tartrate with *dextro*- and *levo*-circularly polarized light, but no excess of one form resulted. This has been shown by Byk to be due to the fact that photochemical reductions can be effected only by the ultra-violet components of sunlight, whereas the alkaline tartrates exhibit circular dichroism only at the red end of the spectrum.

Numerous other attempts to effect selective decomposition of racemates were unsuccessful. In 1929, however, Kuhn and Braun⁵⁴ obtained a faintly active product by the photochemical decomposition of $\text{CH}_3\text{CHCO}_2\text{C}_2\text{H}_5$ with *dextro*- and *levo*-circularly polarized light of



wavelength $\lambda = 2800$, which corresponds to one of the absorption bands of this compound. The rotation, however, was very small, only $\pm 0.05^\circ$. In 1930, more conclusive results⁵⁵ were obtained by the decomposition of α -azidopropionic dimethylamide, $\text{CH}_3\text{CHCON}(\text{CH}_3)_2$.



This molecule has a specific absorption band at $\lambda = 2900$, which is due to the azido group. The *d*- and *l*-forms of this amide exhibited circular dichroism at this wavelength. The *dl*-amide was irradiated with *dextro*-circularly polarized light, and the product was distinctly *dextro*-rotatory ($+0.78^\circ$). Irradiation with *levo*-circularly polarized light gave a *levo*-rotatory product (-1.04°). Hence, it seems to be possible to effect an asymmetric decomposition by means of *d*- and *l*-circularly polarized light, although the products of the decomposition were not isolated or identified. Calculations also showed that only one molecule of the amide was decomposed per quantum of light absorbed. Mitchell⁵⁶ has also effected a similar asymmetric photochemical decomposition of humulene nitrosite, $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_3$, by *d*- and *l*-circularly polarized red light.

The rate at which certain sugars undergo mutarotation has been

⁵³ Cotton, *Ann. chim. phys.*, [7] **8**, 347 (1896).

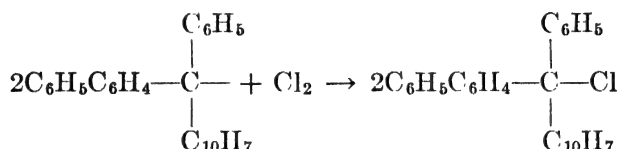
⁵⁴ Kuhn and Braun, *Naturwissenschaften*, **17**, 227 (1929).

⁵⁵ Kuhn and Knopf, *ibid.*, **18**, 183 (1930); *Z. physik. Chem.*, **7B**, 292 (1930).

⁵⁶ Mitchell, *J. Chem. Soc.*, 1829 (1930).

shown by Souty⁵⁷ to be different for *d*- and *l*-circularly polarized light of wavelength 5461 Å. No difference in the rates was observed for light of other wavelengths.

The asymmetric formation of compounds has been studied by several investigators, most of whom obtained negative results. However, Karagunis and Drikos⁵⁸ obtained optically active compounds by the addition of chlorine to triarylmethyl radicals when the reactants were illuminated by circularly polarized light. For example, the following reaction was carried out under the influence of both *d*- and *l*-circularly polarized light at two wavelengths, $\lambda = 4350$ and 5890. At the end of about one hour, a maximum rotation of $+0.08^\circ$ was obtained for the *d*-



circularly polarized light, and -0.08° for the *l*-circularly polarized light. After the reaction had gone to completion, the product was inactive. The *dl*-chloride and the free radical itself were unaffected by either form of circularly polarized light.

Davis and Heggie⁵⁹ have treated 2,4,6-trinitrostilbene (Fig. 37) with bromine under the influence of *d*-circularly polarized light of wavelength 3600–4500 Å. The trinitrostilbene possesses an absorption band in the ultra-violet region, and the bromine exhibits a strong absorption for light of the wavelength used. The formation of excited bro-

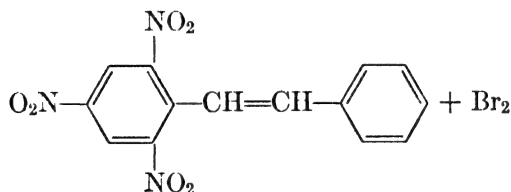


FIG. 37

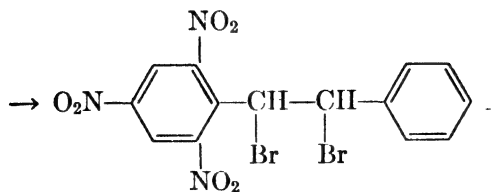


FIG. 38

⁵⁷ Souty, *Compt. rend.*, **199**, 198 (1934).

⁵⁸ Karagunis and Drikos, *Naturwissenschaften*, **21**, 607 (1933); *Nature*, **132**, 354 (1933); *Z. physik. Chem.*, **26B**, 428 (1934).

⁵⁹ Davis and Heggie, *J. Am. Chem. Soc.*, **57**, 377 (1935).

mine atoms at this wavelength has been shown by Mecke.⁶⁰ Hence, conditions were favorable for a reaction between activated bromine atoms and activated trinitrostilbene molecules which led to an optically active dibromotrinitrostilbene (Fig. 38). The rotations observed were low, but beyond experimental error. In benzene as the solvent $\alpha = 0.023^\circ$; in carbon tetrachloride, $\alpha = 0.021^\circ$; in acetic acid, $\alpha = 0.022^\circ$; in nitrobenzene, $\alpha = 0.040^\circ$. The activity was exhibited only after partial reaction had taken place at the end of a certain optimum time interval. After complete reaction, the products were optically inactive. The same reaction mixtures showed no rotation under the influence of plane-polarized light, and exposure of the final product to *d*-circularly polarized light did not cause any activity.

The last two examples of asymmetric syntheses cited are of especial value, since the studies were carried out on well-known reactions, and the products possessed definite structures.

Since sunlight reflected by the sea is partially elliptically polarized, an asymmetrical photochemical agent has been available for ages which could start the chain of asymmetric syntheses of the active compounds found in plants and animals.

PART VI. OPTICAL ISOMERISM OF CYCLIC COMPOUNDS

Compounds Containing Asymmetric Carbon Atoms in the Ring

In number and character, the optical isomers of cyclic compounds with asymmetric carbon atoms forming parts of the ring are, in general, quite similar to the corresponding open-chain compounds. In mono-cyclic compounds with three, four, and five carbon atoms in the ring the number of isomers found agrees with the assumption that these rings are planar and that the groups attached to each carbon atom project above or below the plane of the ring.

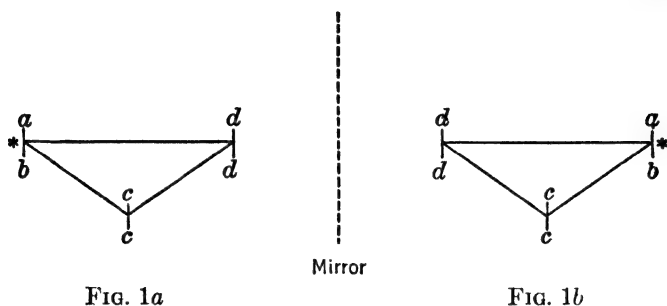
Although rings of six carbons are probably not planar, the isomers observed in such molecules conform to the number calculated on the basis of planarity of the ring. Molecules with rings of more than six atoms have received almost no experimental study from the standpoint of stereoisomerism, but it seems likely that, even though they are non-planar, the number of isomers formed will agree, as in the six-membered ring compounds, with the number expected from a planar ring. The principles just outlined apply equally well to saturated heterocyclic compounds.

Ring compounds differ from open-chain compounds chiefly in that

⁶⁰ Mecke, *Trans. Faraday Soc.*, **27**, 359 (1931).

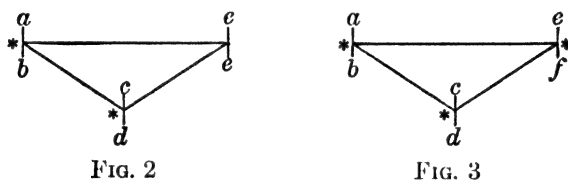
no free rotation between the ring atoms is possible and consequently *cis-trans* isomerism may exist as well as optical isomerism (p. 477).

Three-Membered Rings. A cyclopropane with the general structure of Fig. 1a contains only one asymmetric carbon atom (*) and hence exists in *d*- and *l*-forms represented by Figs. 1a and 1b. The carbon atom



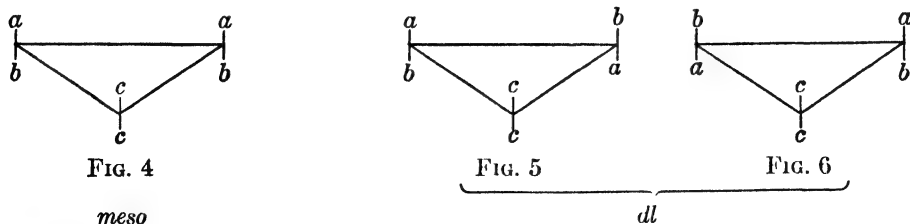
marked with an asterisk is asymmetric, as may be seen by imagining the ring opened between the other two carbon atoms.

The representation of the structures of cyclic compounds by formulas such as those shown in Figs. 1a and 1b is more convenient than using tetrahedra.* If two different asymmetric carbon atoms are present, as in Fig. 2, then four optical isomers are possible which constitute two racemic modifications. Figure 3 shows a molecule with three different



asymmetric carbon atoms which may exist as eight optical isomers or four racemic modifications.

If two like asymmetric carbon atoms are present then a *meso* and a racemic modification may exist. Figure 4 represents the *meso* form, and Figs. 5 and 6 the racemic modification. The *meso* form is a *cis-trans* isomer of the racemic modification.



* Models of the simple cyclic compounds may easily be constructed by cutting triangles, squares, etc., of cardboard and inserting matches at the corners to represent the groups.

In cyclopropane derivatives with the following general structure (Figs. 7-10), carbon atom number 2 is pseudoasymmetric. Two *meso* forms exist shown by Figs. 7 and 8, and two active forms shown by Figs. 9 and 10. These forms, Figs. 7, 8, 9, 10, parallel the forms of the chain

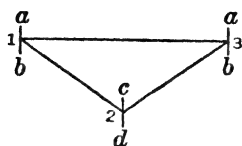


FIG. 7
*meso*₁

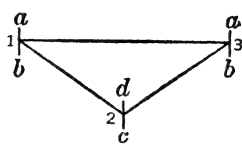


FIG. 8
*meso*₂

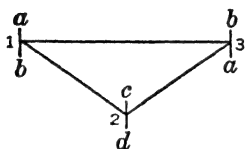


FIG. 9

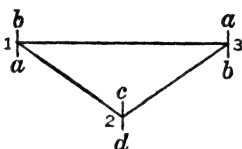


FIG. 10

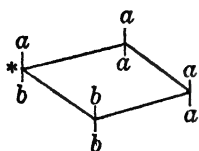
dl

molecule represented by *A-B-A*. From the viewpoint of geometrical isomerism (p. 478) there are three *cis-trans* isomers; one is represented by Fig. 7, one by Fig. 8, and the third *cis-trans* isomer is the racemic modification composed of equal amounts of the *d*- and *l*-forms represented by Figs. 9 and 10. The two *meso* forms and the racemic modification are diastereoisomers of each other and, therefore, have different physical properties and react at different rates with various reagents.

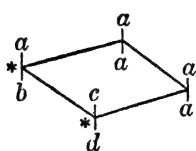
Four-Membered Rings. The number and nature of the stereoisomers of cyclobutane and cyclopentane derivatives can be deduced from considerations of the models of these ring compounds using the same general considerations cited above for the cyclopropane compounds.

The following general formulas represent a summary of the isomers existing in cyclobutane derivatives substituted in the manner indicated (Figs. 11-22).

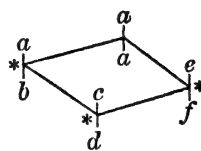
Molecules of the type shown in Fig. 22 are represented by the five truxillic acids which are formed by the dimerization of *trans*-cinnamic



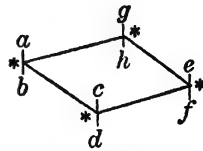
1 *dl*-form
FIG. 11



2 *dl*-forms
FIG. 12



4 *dl*-forms
FIG. 13



8 *dl*-forms
FIG. 14

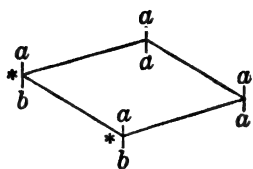
1 *dl*-form1 *meso*

FIG. 15

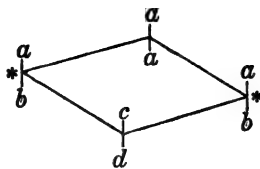
1 *dl*-form2 *meso*

FIG. 16

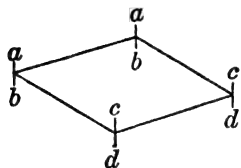
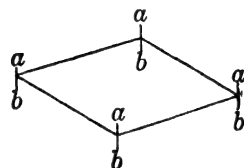
4 *dl*-forms2 *meso*

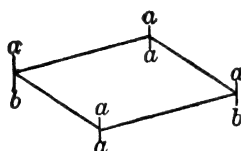
FIG. 17



No optical isomers

4 *cis-trans* forms

FIG. 18



No optical isomers

2 *cis-trans* forms

FIG. 19

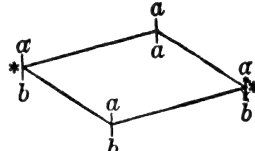
1 *dl*-form2 *meso*

FIG. 20

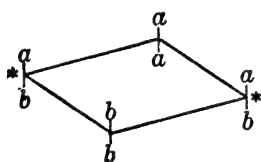
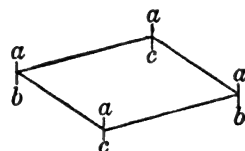
1 *dl*-form1 *meso*

FIG. 21



No optical isomers

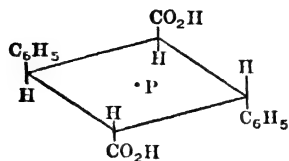
5 *cis-trans* forms

FIG. 22

acid. Each of them is identical with its mirror image, although α -truxillic acid (Fig. 23), unlike the other four isomers, has no plane of symmetry. Its symmetry results from the fact that when, from any atom in the molecule, a line is drawn to the point P and extended an equal distance beyond, it meets an atom identical to the one at its origin. Any molecule possessing such a point, called a *center of symmetry*, is identical with its mirror image.

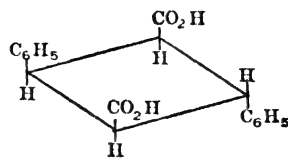
Another unusual element of symmetry must be postulated for mole-

cules in which the *b* groups of Fig. 18 are present as enantiomorphic pairs. Figures 28–32*a* represent some (but not all) of the isomers possible for this case.



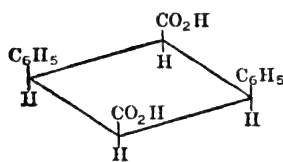
α -form, m.p. 274°

FIG. 23



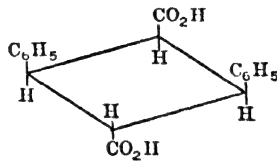
γ -form, m.p. 288°

FIG. 24



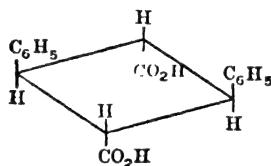
peri-form, m.p. 266°

FIG. 25



epi-form, m.p. 285°

FIG. 26



ϵ -form, m.p. 189°

FIG. 27

Each of the compounds, Figs. 28 and 31, has a plane of symmetry. The compounds of Figs. 29 and 30 are asymmetric and together constitute a racemic pair. Although the compound of Fig. 32*a* possesses

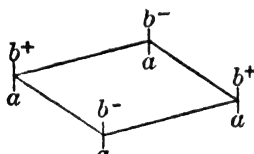


FIG. 28

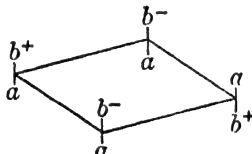


FIG. 29

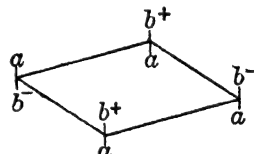


FIG. 30

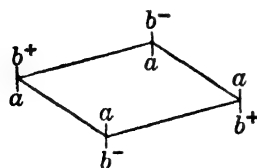


FIG. 31

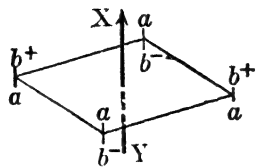


FIG. 32*a*

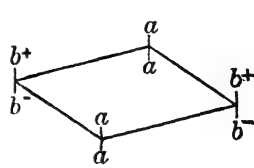


FIG. 32*b*

none of the symmetry elements previously described, nevertheless it is identical with its mirror image. Examination of its structure shows that,

when the groups below the plane of the ring are rotated 90° in a plane parallel to the plane of the ring, about an axis, XY perpendicular to the ring at the center, the mirror images of the respective groups appear above them as shown in Fig. 32b. Such an axis, XY has been termed an *alternating axis of symmetry*—the term arising from the fact that enantiomorphic groups in the original molecule, Fig. 32a, *alternate successively* above and below the plane of the ring. The concept is limited to cyclic compounds with a perfectly symmetrical alternating distribution of groups around the ring. Thus Fig. 32c contains an alternating axis of symmetry but Fig. 32d does not. Olefins may be regarded as two mem-

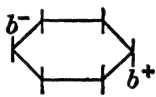


FIG. 32c

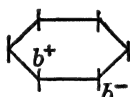


FIG. 32d

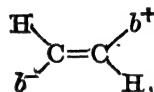


FIG. 32e

bered rings so that Fig. 32c has an alternating axis of symmetry but neither a plane nor a point of symmetry.

Five-Membered Rings. The isomeric forms of substituted cyclopentanes indicate that the five carbon atoms of the ring are also in one plane.

The furanose forms of the sugars constitute important examples of heterocyclic five-membered rings (Figs. 33a, 33b). The γ -lactones (Figs. 33c, 33d) are also important five-membered ring compounds.

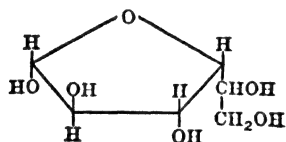
 β -Gluconofuranose

FIG. 33a

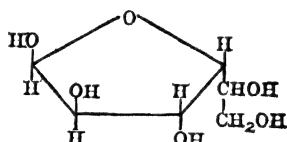
 α -Gluconofuranose

FIG. 33b

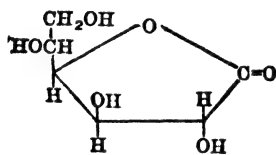
 γ -Gluconolactone

FIG. 33c

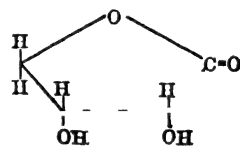
*d*-Erythrulose

FIG. 33d

Six-Membered Rings. The status of cyclohexane derivatives cannot be regarded as settled. The study of the chemical and physical properties of rings containing six or more atoms has shown that such ring systems may not be planar. Examination of the isomeric forms of fused ring systems (p. 328), and construction of the models of such compounds, have shown that the carbon atoms in six or more membered rings unite in a manner involving the minimum deviation from the regular tetra-

hedral angle, and hence, according to Sachse and Mohr, form "strainless rings" (p. 69).

The models of cyclohexane indicate that two forms are possible. These are the "boat or C-form" (Fig. 34 or 34a), and the "chair or Z-form" (Fig. 35 or 35a). However, no isomeric forms of cyclohexane or its

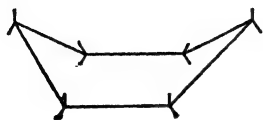


FIG. 34

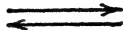


FIG. 35



FIG. 34a



FIG. 35a

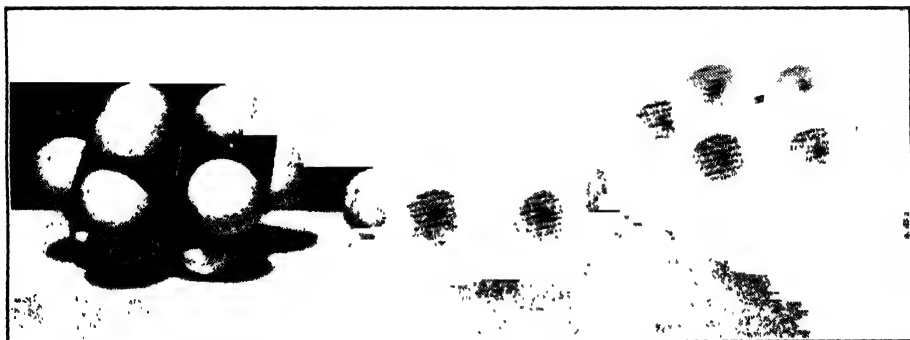


FIG. 34b.

FIG. 34c.

FIG. 34d.

derivatives have been isolated with certainty up to the present time. It seems probable that there is an equilibrium between the two forms of such molecules and that the two structures vibrate from one to the other so rapidly that the net average result is a planar molecule.

Stuart¹ has constructed atomic models which represent the atoms in their relative sizes as deduced from x-ray data. They are so formed that, when appropriate atoms are linked together into a molecule, the relative interatomic distances are maintained in the structure. A photograph of the boat form of cyclohexane is shown in Fig. 34d. Benzene is shown in Fig. 34c for comparison. When attempts are made to build the chair form of cyclohexane the peculiar-appearing strainless model of Fig. 34b results. Although very useful and instructive, the Stuart models have been found in practice to represent the structures of molecules in

¹ Stuart, *Z. physik. Chem.*, **B27**, 350 (1927).

more compact form than actually exists. Thus the conversion of the boat to the chair form of cyclohexane involves a much greater strain using these models than the chemical study of cyclohexane would lead one to believe.

By mathematical analysis Brodetsky² believes the Z-form of the methyl cyclohexane ring can give rise to two isomeric monosubstituted derivatives, while Henriquez³ deduces one fixed Z-modification and an infinite number of mobile modifications of which the C-form is one.

The existence of boat and chair isomers would be possible only if the substituents were of such nature as to cause the stabilization of the positions of the atoms constituting the ring. The only examples of such a stabilization have been found among fused ring systems, which will be discussed in the next section. The numerous attempts, on the other hand, to find substituents which will cause a fixation of the two forms in monocyclic compounds have failed to yield convincing results.

In a monosubstituted cyclohexane, such as cyclohexanol, the boat form appears to exhibit position isomerism (Figs. 36, 38, 39), geometric isomerism (Figs. 36 and 37, 38 and 40, 39 and 41), and optical isomerism



FIG. 36



FIG. 37

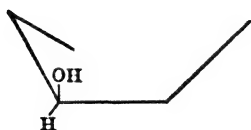


FIG. 38

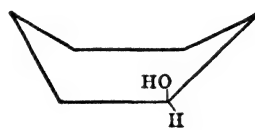


FIG. 39

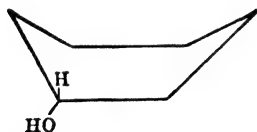


FIG. 40

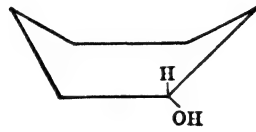


FIG. 41

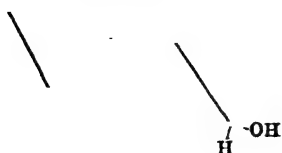


FIG. 42



FIG. 43

² Brodetsky, *Proc. Leeds Phil. Lit. Soc.*, I, 370 (1929); Wightman, *Chemistry & Industry*, 58, 604 (1939).

³ Henriquez, *Proc. Acad. Sci. Amsterdam*, 37, 532 (1934).

(Figs. 38 and 39, 40 and 41). Actually, however, each of the forms 36–41, inclusive, is convertible into the other without the necessity of passing through a strained configuration; rotation is as free in these forms of strainless rings as in an open-chain molecule. In the chair form, however, the structure is rigid, so that the two possible isomers (Figs. 42 and 43) cannot be converted into each other without momentarily, at least, adopting a strained configuration. Moreover, the conversion of a chair to a boat form involves some degree of strain. In an attempt to isolate chair and boat isomers, Wightman⁴ converted 1-carbomethoxycyclohexylformic acid (Fig. 44) into 1-carbomethoxycyclohexylformamide (Fig. 45) by two methods, one involving the conversion of the

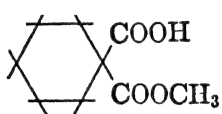


FIG. 44

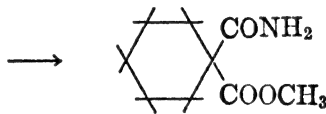


FIG. 45

carboxyl group of Fig. 44 to the amide and the other the conversion of the ester group to the amide and esterification of the carboxyl. Two compounds, bearing the same relationship to each other as do the cyclohexanols of Figs. 42 and 43 or of Figs. 36 and 37, were produced. The two proved to be identical, showing that such isomers, if they exist at all, must be present as an equilibrium mixture.

A planar model of 4-methyl-1-carboxycyclohexylacetic acid (Fig. 46) possesses two *cis-trans* isomers (Figs. 47 and 48). A strainless ring model has theoretically eight possible forms (Figs. 49–56) on the basis of one chair form and one boat form of cyclohexane.*

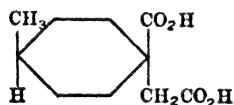


FIG. 46

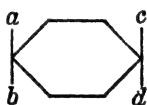


FIG. 47

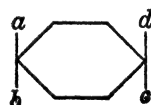


FIG. 48

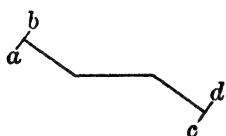


FIG. 49

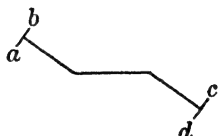


FIG. 50

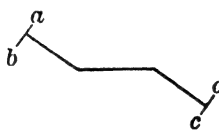


FIG. 51

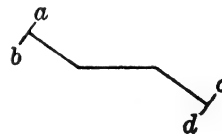


FIG. 52

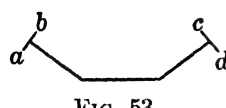


FIG. 53

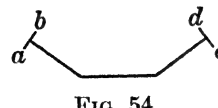


FIG. 54

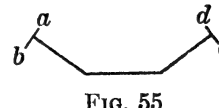


FIG. 55

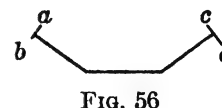


FIG. 56

⁴ Wightman, *J. Chem. Soc.*, 2543 (1926).

* The student should satisfy himself on these points by a study of the models.

M. Quadrat-I-Khuda ⁵ reported four isomers of the compound shown in Fig. 46, but Goldschmidt ⁶ found that two of the isomers reported by Khuda were merely molecular compounds of the other two. Miller and Adams ⁷ obtained further evidence from a study of 4,4-dimethyl-1-carboxycyclohexylacetic acid and 4,4-dimethylcyclohexyl-1,1-diacetic acid that isomers of this type do not exist.

Vogel ⁸ has reported having obtained methyleyclohexanes in C- and Z-forms depending on the mode of preparation. From pure 2-, 3-, or 4-methyleyclohexanones, by Clemmensen reduction, he obtained a single stable methyleyclohexane (d_4^{20} 0.7693, n_D^{20} 1.42316) identical with that resulting from the dehydration of 2-methyleyclohexanol followed by reduction. However, the methyleyclohexane prepared by a modified Wolff-Kishner reduction of the pure 2- and 4-cyclohexanone semicarbazones had the following constants, d_4^{20} 0.7676, n_D^{20} 1.42311, and upon standing several days or more rapidly upon warming changed to a product with constants d_4^{20} 0.7695, n_D^{20} 1.42326. Vogel interpreted these results as isolation of an unstable and a stable form of methyleyclohexane representing C- and Z-modifications. The acceptance of these conclusions must await confirmation and further experimentation.

Up to the present, therefore, no conclusive evidence is available to suggest the calculation of the number of isomers of a monocyclic ring system with six atoms except on the basis of a planar ring. Thus, the same conditions obtain as in the three-, four-, or five-membered ring compounds and the number of isomers is dependent on the number of asymmetric carbon atoms present. If the asymmetric carbon atoms are all different from each other the number of isomers is equal to 2^n (where n = number of asymmetric carbon atoms).

Limonene is an example of a compound with one asymmetric carbon atom. It exists in a *d*- and an *l*-form, Figs. 57 and 58.

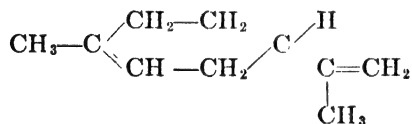


FIG. 57

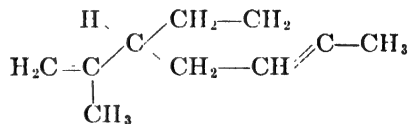


FIG. 58

The racemic modification is known as dipentene.

Hexahydro-*o*-toluic acid (Fig. 59) is an example of a cyclohexane derivative with two different asymmetric carbon atoms. It, therefore,

⁵ Quadrat-I-Khuda, *J. Indian Chem. Soc.*, **8**, 277 (1931); *Nature*, **132**, 110 (1933); **136**, 301 (1935).

⁶ Goldschmidt and Gröfing, *Ber.*, **69**, 279 (1935).

⁷ Miller and Adams, *J. Am. Chem. Soc.*, **58**, 787, 2659 (1936).

⁸ Cowan, Jeffery, and Vogel, *J. Chem. Soc.*, 1862 (1939); see, also, Vogel, *ibid.*, 333 1758 (1934); 1323 (1938).

exists in two racemic modifications. The same number of racemic forms exists for hexahydro-*m*-toluic acid (Fig. 60), but the *para* compound (Fig. 61) does not possess any optical isomers, since this molecule has no asymmetry. It does exist in two geometric forms.

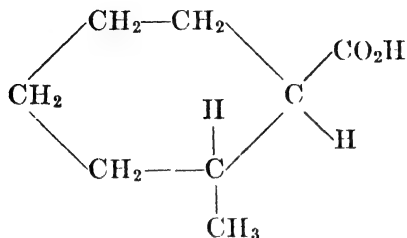


FIG. 59

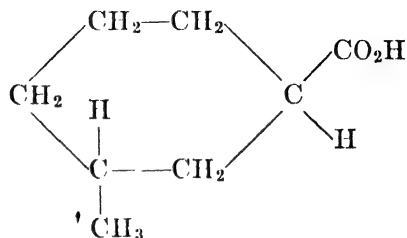


FIG. 60

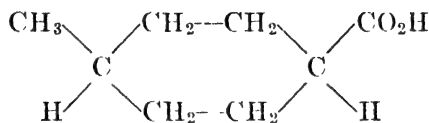
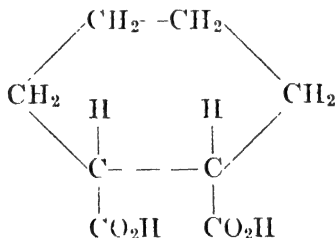


FIG. 61

The hexahydrophthalic acids illustrate cyclic compounds with two similar asymmetric carbon atoms. Figure 62 represents the *meso* or *cis*

FIG. 62
meso or *cis*

form, and Figs. 63 and 64 the *d*- and *l*-forms of the racemic modification which is *trans*.

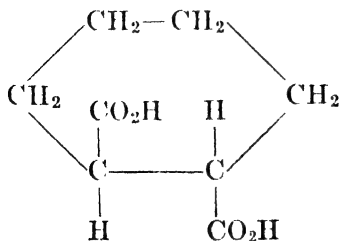


FIG. 63

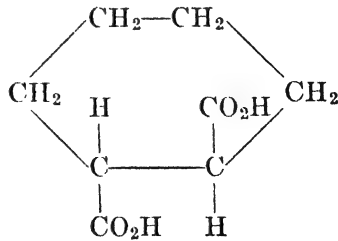


FIG. 64

Racemic or *trans*

Hexahydroisophthalic acid (Fig. 65) also exists in *meso* and racemic modifications. The isomerism of these compounds hence parallels that of tartaric acid (p. 232). Hexahydroterephthalic acid (Fig. 66) possesses

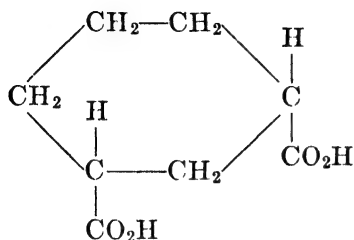


FIG. 65

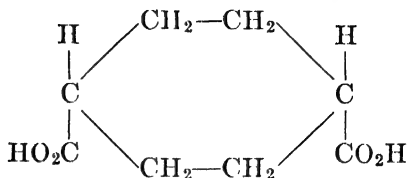


FIG. 66

no asymmetric carbon atoms and a plane of symmetry, and hence does not have any optical isomers.

Menthol is an example of a cyclic compound with three different asymmetric carbon atoms (Fig. 67). Eight optical isomers are possible,

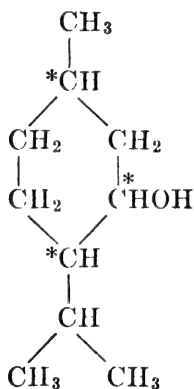


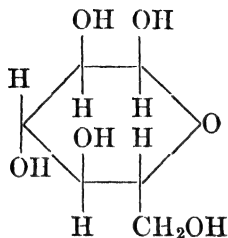
FIG. 67

existing as four racemic modifications. The common form, *l*-menthol ($[\alpha]_D -54.75^\circ$), is the chief constituent of oil of peppermint.

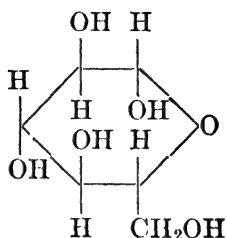
The normal or pyranose forms of the sugars constitute important examples of heterocyclic six-membered rings containing five different asymmetric carbon atoms. Figures 68 and 69 represent the formulas of α - and β -glucose. These two forms are diastereoisomers. Since there are five different asymmetric carbon atoms in the glucopyranose ring, a total of thirty-two optical isomers which constitute sixteen racemic modifications is possible.

The substituted diketopiperazines illustrate another type of six-membered heterocyclic ring. Alanyl anhydride or 2,5-dimethyldike-

topiperazine contains two like asymmetric carbon atoms and hence exists in an inactive or *meso* form, and two optically active forms con-



α -Glucose
FIG. 68



β -Glucose
FIG. 69

stituting a racemic modification. Figure 70 represents the *meso* or inactive form, and Figs. 71 and 72 the mirror images of the racemic

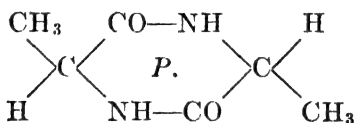


FIG. 70
meso

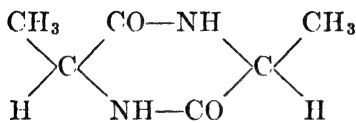


FIG. 71

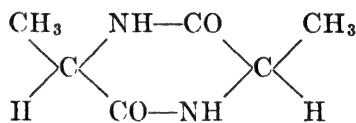


FIG. 72

dl

modification. Examination of these three structures shows that none of them possesses a plane of symmetry. Construction of the mirror image of the model of Fig. 70, in which the methyl groups are in the *trans* position, however, shows that the mirror image is identical with the original.

The molecule shown in Fig. 70 constitutes another example of a compound with a center of symmetry (p. 318). The molecules shown in Figs. 71 and 72 do not possess such a center of symmetry.

Many-Membered Rings. Substituted rings containing more than six members have received little attention from the viewpoint of stereochemistry. Evidence favors the conclusion that the same number of optical isomers will exist as may be calculated on the basis of a planar ring.

An interesting experiment was performed in an attempt to resolve the semicarbazide of cyclononanone. The Stuart models represent this

molecule as so compact that the mirror images are not interconvertible. The resolution failed,⁹ however.

Fused Ring Systems

For convenience in discussion and determination of the number of isomers, compounds containing fused rings may be classified into the following groups.

1. Alicyclic compounds in which the rings are fused through adjacent atoms.
 - (a) Two five- (or more) membered rings fused through adjacent atoms.
 - (b) Three five- or six-membered rings fused through adjacent atoms.
 - (c) Two rings fused through adjacent atoms, one ring of which is highly strained (contains three or four atoms).
 - (d) Molecules containing several rings fused through adjacent atoms.
2. Alicyclic compounds containing five- or six-membered rings fused through non-adjacent atoms.
3. Fused systems containing rings of more than six members.
4. Molecules containing more than two fused rings.

Group 1a. The same rules which are used to determine the number of isomers in monocyclic compounds apply to substances in group 1a. Thus, 3,3,0-bicycloöctane (Fig. 73) which has no asymmetric carbons exists in a *cis* form (Fig. 74) and a *trans* form (Fig. 75); hexahydrohydrindane (Fig. 76) which possesses two similar asymmetric carbons exists in a *meso-cis* (Fig. 77) and a *racemic-trans* form (Fig. 78); methylhexahydrohydrindane (Fig. 79), which possesses two different asymmetric carbon atoms, exists in a *racemic-cis* (Fig. 80) and a *racemic-trans* form (Fig. 81); and decalin (Fig. 82) with no asymmetric carbon atoms exists in a *cis* (Fig. 83) and a *trans* form (Fig. 84).

The existence of the *trans* isomers of these substances affords the most conclusive evidence for the strainless configuration of rings containing five or more atoms. These structures follow logically the use of the tetrahedral carbon atoms in their construction. They are discussed in some detail elsewhere (p. 484).

Optical isomerism is found only in the *trans* form of hexahydrohydrindane (Fig. 78) and in the *cis* and *trans* forms of methylhexahydrohydrindane (Figs. 80 and 81) as it is only these forms which possess non-superimposable mirror images.

⁹ Marvel and Glass, *J. Am. Chem. Soc.*, **60**, 1051 (1938).

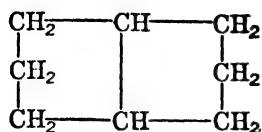


FIG. 73

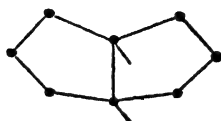


FIG. 74



FIG. 75

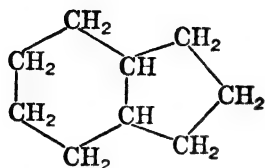


FIG. 76



FIG. 77

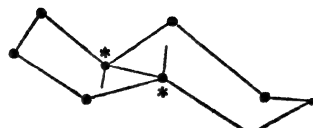


FIG. 78

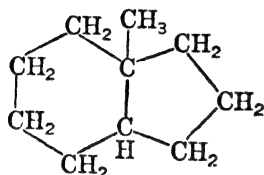


FIG. 79

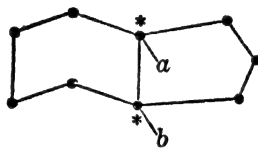


FIG. 80

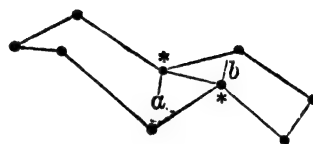


FIG. 81

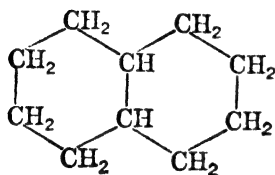


FIG. 82



FIG. 83

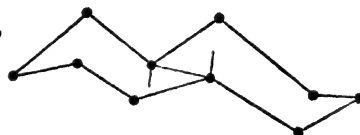


FIG. 84

The decahydro- α - and - β -naphthols (Figs. 85 and 86) and decahydro- β -naphthylamine (Fig. 87) constitute examples of fused strainless rings possessing three asymmetric carbon atoms (marked *). Each of these compounds may exist in eight optically active isomers (2^3) which constitute four racemic modifications, all of which have been isolated.

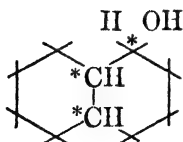


FIG. 85

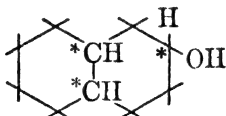


FIG. 86

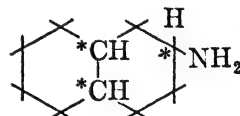


FIG. 87

In view of the fact that molecules containing two fused rings of the type just discussed are of very common occurrence, a generalization concerning the possible number of isomers is desirable. It is assumed in these generalizations that no asymmetry is present in either ring which would necessarily increase the number of possible isomers.

A compound containing two *similar* unsubstituted rings of five or more members, fused through two adjacent atoms, may exist in two geometric forms, a *cis* and *trans*, both of which will be inactive and incapable of resolution owing to the absence of asymmetry in the molecules.

If the two *similar* rings are substituted either on the fusion atoms or in the rings and the substituents are so placed that neither of the two fusion carbon atoms is asymmetric the *cis* and *trans* forms will also be inactive and incapable of resolution.

If the substituents are so placed that the two fusion atoms are asymmetric and identical, the *cis* and the *trans* forms may be either *meso* or racemic, depending upon the positions of the substituents. Such examples are shown in Figs. 88 and 89. The *trans* form of Fig. 88 is *meso*; that of Fig. 89 is racemic.

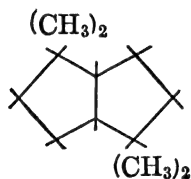


Fig. 88

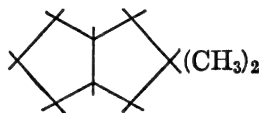


Fig. 89

If the substituents are so placed that the two fusion atoms are asymmetric and not identical, both the *cis* and *trans* forms will be racemic.

A compound containing two unsubstituted rings, each of a different size and each of five members or more, fused through adjacent atoms may exist in *cis* and *trans* forms; the fusion atoms will be asymmetric and identical, and consequently the *cis* form will be *meso* and the *trans* form racemic. The introduction of substituents in the molecule, either on the fusion atoms or in the rings, may also lead to fusion atoms which are asymmetric and identical and result in *cis-meso* and *trans-racemic* forms. If, however, the substituents are so placed as to cause the fusion atoms to be asymmetric and not identical, both the *cis* and *trans* forms will be racemic.

Group 1b. If three *five-* or *six-*membered rings are fused through the same two adjacent carbon atoms, a rigid structure results as shown in Fig. 90.

No *cis* and *trans* isomers can exist since interchange of two of the linkages at each of the fusion carbon atoms would involve impossible strains. In the existing form shown, optical isomerism may occur only when each of the three rings is different from the others since only in such molecules are the elements of symmetry absent.

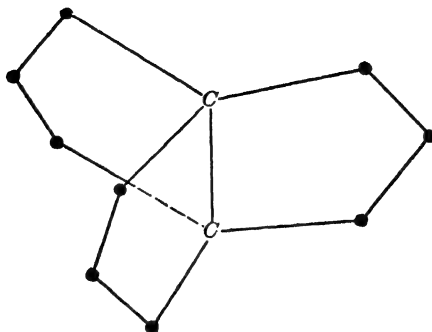


FIG. 90

Group 1c. In a molecule with two rings fused through two adjacent carbon atoms, one ring of which is highly strained as in three- or four-membered rings, only one geometric form is found. Thus, in cyclohexene oxide (Fig. 91), a six-membered cyclohexane ring and a three-membered ethylene oxide ring are fused together. As the two hydrogens are on one side of the six-membered ring and the oxygen on the other, Fig. 91 represents a *cis* modification which is *meso*. The hypothetical *trans* form is shown in Fig. 92. The hydrogens on opposite

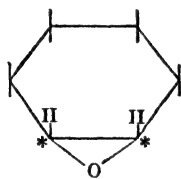


FIG. 91

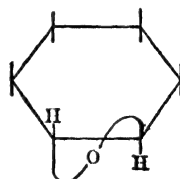


FIG. 92

sides of the six-membered ring necessitate a linking of the valencies of the oxygen atom through *trans* positions. This structure involves such a tremendous strain that this isomer cannot exist. Hence, only one form of cyclohexene oxide is known, the *cis* or *meso* form.

If the restraining effect of either of the rings is removed by opening them, the normal number of forms is obtained. For example, the glycol, Fig. 93, exists in a *meso* or *cis* form and a *trans* or racemic modification. 2-Chlorocyclohexanol (Fig. 94) may exist in four optically active forms composed of two racemic modifications, but treatment with alkali yields only one inactive cyclohexene oxide. These examples illustrate the freedom conferred on the groups by the removal of the three-membered ethylene oxide ring.

Removal of the cyclohexane ring leads to ethylene oxide which, of course, cannot exist in stereoisomeric forms, but its carboxylic acid

derivatives can. Thus Fig. 95 represents the *meso* form and Fig. 96 the *trans* or racemic modification of ethylene oxide dicarboxylic acid. Both forms are known. The *meso* and racemic forms of 2,3-epoxybutane have also been obtained.

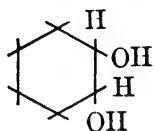


FIG. 93

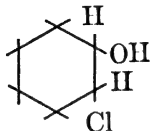


FIG. 94

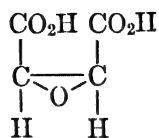


FIG. 95

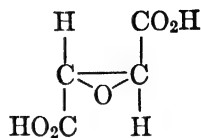


FIG. 96

For the present discussion a cyclic molecule containing a double bond in the ring may be considered a type of double ring system fused on adjacent carbons, one ring of which merely has two atoms. As a result of the previous considerations the same situation should obtain as in fused ring molecules containing one highly strained ring. Existence of a single geometric form, a *cis* modification, would be expected; thus cyclohexene or cyclopentene may be cited as examples, each of which has been isolated in a single form only. The olefinic ring must be of sufficient size (p. 336) to allow the *trans* modification of the olefin to be formed without appreciable strain before both geometric isomers may be anticipated. No such compounds have been obtained experimentally.

Group 1d. When several rings are present in a molecule, each fused to the next one through two adjacent atoms, the stereochemistry of each individual substance must be considered independently. The strains in compounds of this kind will be contingent upon the fashion in which the rings are fused. Actually the number of isomers which can exist will usually be much smaller than that calculated on the basis of the asymmetric carbon atoms present. Thus, dihydrocholesterol (Fig. 97) repre-

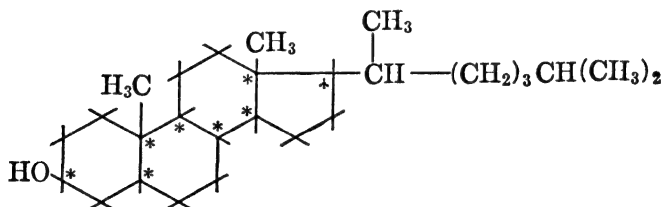


FIG. 97

sents a fused system of rings. Inspection of the formula shows the presence of nine asymmetric carbon atoms, six of which are fusion atoms. The theoretical number of possible optical isomers is 512, but only a small fraction of these may actually be constructed without strains greater than are ordinarily found in organic molecules. The bile acids,

the sex hormones, the various reduced sterols, and their derivatives (p. 1341) constitute important examples of fused ring systems.

Group 2. The fusion of two strainless five- or six-membered rings through non-adjacent atoms also leads to a rigid structure which does not permit the formation of all the isomers calculated on the basis of the number of asymmetric carbon atoms. The stereochemistry of such compounds can best be understood by consideration of specific examples.

The structural formula of camphor has been shown to be that of Fig. 98. Examination of the formula shows that carbon atoms 1 and 4 are attached to four different groups and hence asymmetric. The presence of two different asymmetric carbon atoms would normally lead to the prediction of four optical isomers. However, construction of this molecule using tetrahedral carbon atoms reveals the fact that only one arrangement of the rings about the fusion carbon atoms is accompanied with essentially no strain. The other form in which two bonds on each of the fusion carbon atoms are interchanged would impose an impossible strain upon the rings. Camphor, therefore, exists in only a *d*- and *l*-modification. Schematic projections of the space model are represented in Figs. 99 and 100. Both forms occur naturally, and an equimolecular mixture of the two constitutes *dl*-camphor.

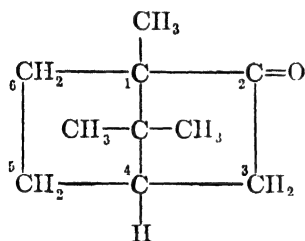


FIG. 98

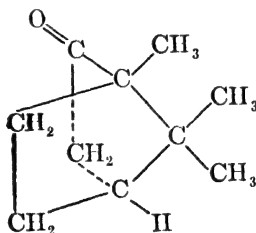


FIG. 99

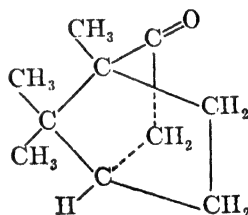


FIG. 100

Reduction of the keto group of camphor to the secondary alcohol group generates a new asymmetric carbon atom (Number 2) (Fig. 101). Since this carbon atom may give rise to *d*- and *l*-forms a total of four

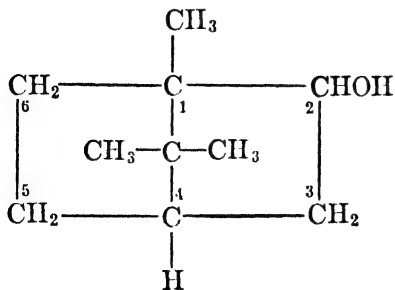


FIG. 101

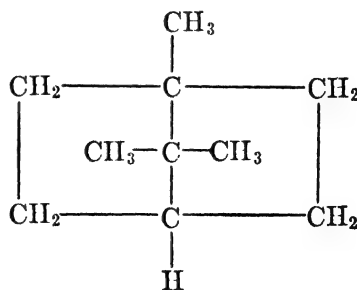


FIG. 102

optically active forms should exist, as in fact they do. Both *d*- and *l*-borneol, and *d*- and *l*-isoborneol are known.

Complete reduction of camphor or the borneols leads to camphane (Fig. 102), which cannot exist in optically active isomeric forms since it possesses a plane of symmetry.

Cocaine is another molecule of this sort. It is a naturally occurring alkaloid whose structure is represented in Fig. 103. Two asymmetric carbons, numbers 2 and 6, are involved in the rigid fusion of the pyrroli-

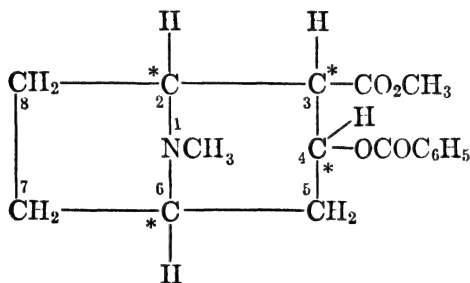


FIG. 103

dine and piperidine rings and consequently lead to a single geometric form, which is racemic. With two additional asymmetric carbons present 2^3 or 8 active forms constituting four racemic modifications may be expected.

Two six-membered rings may be fused through adjacent atoms, through atoms with one carbon atom between, or through atoms separated from each other by two carbon atoms as shown in Fig. 104.

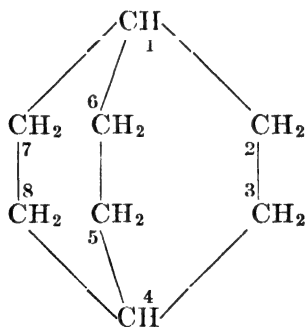


FIG. 104

Substances in this group are no different from those previously described. Only one geometric form is possible on account of the strain involved in the isomer. Since the molecule in Fig. 104 is symmetrical, it is obvious that no optical isomerism can exist. This condition still

holds if the fusion carbon atoms 1 and 4 hold different groups or if one of the rings is made different from the others by substitution, for example, of two methyl groups in the 2-position. Only if each ring differs from the other two is symmetry destroyed and optical isomerism becomes possible. This may be illustrated by a molecule in which two methyls are substituted on carbon 2 or 3 and two ethyls on carbon 5 or 6.

An important specific example of this type of fused ring system is the substituted quinuclidine nucleus which occurs in quinine and cinchonine (p. 1202). Inspection of the structure of quinine (Fig. 105) shows the

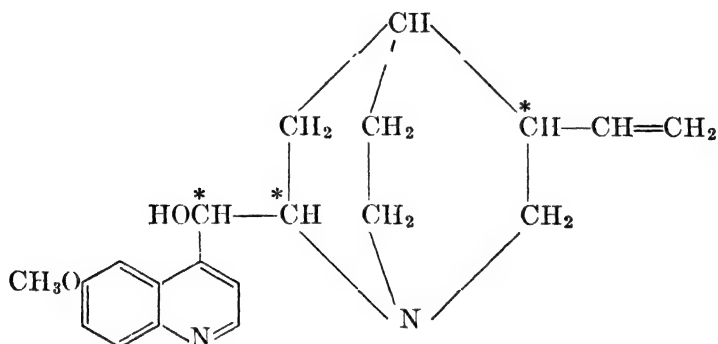


FIG. 105

presence of a bicyclic nucleus similar to that of Fig. 104 in which one of the fusion carbon atoms has been replaced by nitrogen. This causes the same type of rigidity in the molecule and eliminates the *trans* form. As a consequence, this fused ring system in conjunction with three other asymmetric carbon atoms makes possible the existence of 2^4 or 16 optical isomers of which the naturally occurring alkaloid is one.

Various combinations of five- and six-membered rings are obviously possible. All molecules of this type exist in only one geometric form, and the presence of optical isomerism in this form will depend upon whether the molecule has elements of symmetry.

Group 3. The molecules discussed in groups 1b, 1c, 1d, and 2 have been limited to saturated rings of five and six members. If double bonds are introduced into the ring systems in groups 1a, b, c, d, and 2 the strains may be considerably modified and the number of isomers may be less than it would otherwise be. This is especially true in complicated molecules with several fused rings.

It has been clearly demonstrated experimentally that five- and six-membered rings with allene or acetylene linkages cannot be prepared. On the other hand, a seven-membered ring containing an allene linkage¹⁰

¹⁰ Favorsky, *Bull. soc. chim.*, [5] 3, 1727 (1936)

has been reported (Fig. 106) and a fifteen- and a seventeen-membered ring containing an acetylene linkage¹¹ (Fig. 107). This suggests that, in all probability, in fused ring systems, both *cis* and *trans* isomers may be anticipated provided that one or both rings are of such size that interchange of linkages at the fusion carbon atoms may occur without serious strain (Figs. 108 and 109). The number of geometric and optical isomers

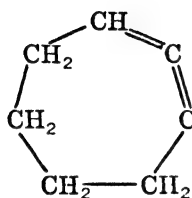


FIG. 106

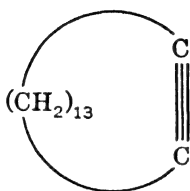


FIG. 107

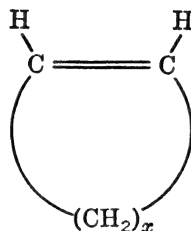


FIG. 108

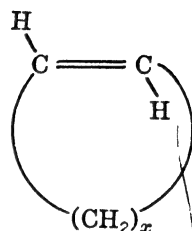


FIG. 109

will then be coincident with that calculated on the basis of strainless models. These predictions have not been tested experimentally.

Group 4. Many natural and synthetic compounds contain more than two fused rings. The general principles of stereoisomerism involved in these systems are the same as those in molecules with two fused rings. However, each additional ring fused to the molecule modifies to a certain extent the individual strains in each ring. Although theoretical considerations make possible a large number of stereoisomers in such complex molecules, actually very few forms exist. The limited number is probably due to the strains involved in the formation of such isomers.

PART VII. OPTICAL ISOMERISM OF COMPOUNDS CONTAINING NO INDIVIDUAL ASYMMETRIC ATOMS

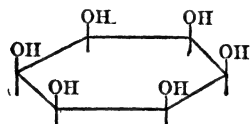
As mentioned in the opening sections, an asymmetric atom is only one source of asymmetry in molecules. Several types of molecules are known whose asymmetry is due to their *structure as a whole*. Specific examples of each type will be considered in order to illustrate the nature of the asymmetry of such molecules.

Inositol Type. Inositol is hexahydroxycyclohexane. It occurs in plants as a hexaphosphoric ester known as phytin.

There are eight possible geometrical isomers of inositol, but only one of these isomers has a mirror image which is non-superimposable. The two enantiomorphs are shown in Fig. 8 and the other geometrical isomers in Figs. 1 to 7.

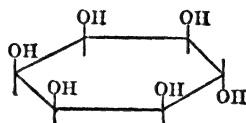
¹¹ Ruzicka, Hürbin, and Boekenoogen, *Helv. Chim. Acta*, **16**, 498 (1933).

None of the three elements of symmetry previously discussed is present in the form, Fig. 8. Both the *d*- and *l*-forms ($[\alpha]_D \pm 65^\circ$) of inositol were described by Mohr¹ in 1903. The structures of the remaining isomers have not been established with certainty.²



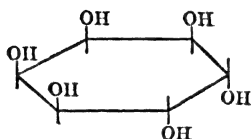
6 planes of
symmetry

Fig. 1



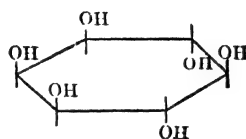
1 plane of
symmetry

Fig. 2



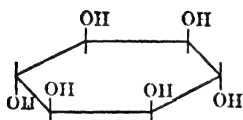
1 plane of
symmetry

Fig. 3



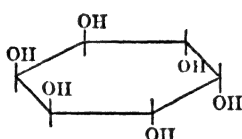
1 plane of
symmetry

Fig. 4



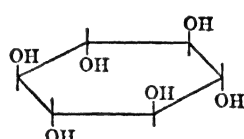
2 planes of
symmetry

Fig. 5



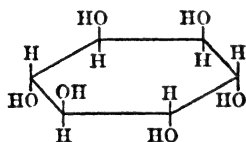
1 plane of symmetry
Center of symmetry

Fig. 6

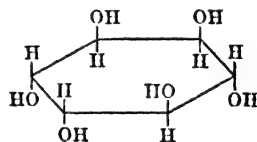


3 planes of symmetry
Center of symmetry

Fig. 7



d



l

dl-Inositol

Fig. 8

Allenes. In his discussion of the spatial distribution of the valence forces about the carbon atom, van't Hoff³ in 1875 pointed out that an

¹ Mohr, *J. prakt. Chem.*, [2] **68**, 369 (1903).

² Posternak and Posternak, *Helv. Chim. Acta*, **12**, 1165 (1929).

³ van't Hoff, "Die Lagerung der Atome im Raum," Vieweg und Sohn, Braunschweig (1908).

allene of the formula shown in Fig. 9 should be capable of existing in the optically isomeric forms shown in Figs. 10 and 11 if the carbon atom possesses a tetrahedral configuration. Examination of the models of Figs. 10 and 11 shows that they possess no plane of symmetry. The groups *ab* and *cd* do not lie in the same plane, and the structures of Figs. 10 and 11 are non-superimposable mirror images.

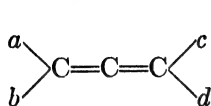


FIG. 9

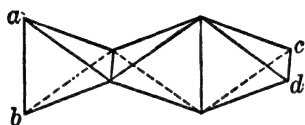


FIG. 10

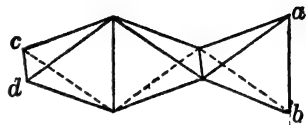


FIG. 11

dl-Modification

Somewhat later it was pointed out that any allene with two different groups on each of the terminal carbon atoms should be capable of existing in optically isomeric forms, Figs. 12, 13, and 14. It is not necessary that four different groups be present as in Fig. 9.

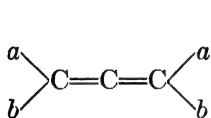


FIG. 12

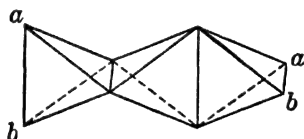


FIG. 13

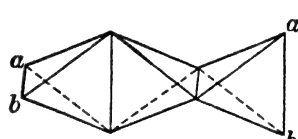


FIG. 14

dl-Modification

Following these theoretical predictions numerous attempts were made to prepare allenes containing groups which not only would fulfill the necessary stereochemical requirements but also would contain reactive groups permitting resolution.

It was not until 1935, sixty years after van't Hoff's prediction, that experimental verification was secured. Mills and Maitland⁴ in 1935 accomplished a catalytic asymmetric dehydration of the alcohol shown in Fig. 15 by means of the optically active camphorsulfonic acids.

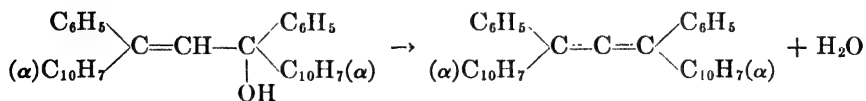


FIG. 15

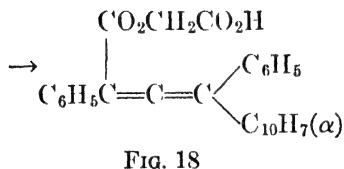
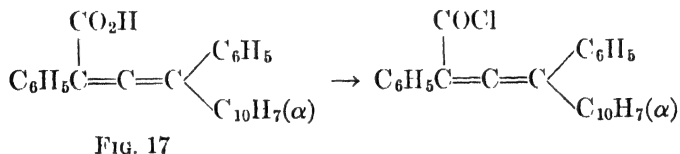
FIG. 16

When the dehydration was carried out with an optically inactive catalyst the racemic form (m.p. 244°) of the allene in Fig. 16 resulted

⁴ Mills and Maitland, *Nature*, **135**, 994 (1935); *J. Chem. Soc.*, 987 (1936).

When the alcohol of Fig. 15 was boiled with a 1 per cent benzene solution of *d*-camphor-10-sulfonic acid an optically active allene was obtained which had a rotation of $[\alpha]_{5461}^{20} + 437^\circ$. Similarly treatment of the alcohol with *l*-camphor-10-sulfonic acid gave the *levo*-rotatory allene $[\alpha]_{5461}^{20} - 438^\circ$. The optically active isomers melted at 159° . When mixed and crystallized from a solvent the resulting racemic compound melted at 244° . Mills and Maitland proved by several methods that the products obtained by dehydration of the alcohol of Fig. 15 were allenes and not substituted indenenes.

Kohler, Walker, and Tishler ⁵ completed the first actual resolution of the racemic form of an allene. In 1910 Lapworth and Wechsler ⁶ prepared the allenic acid shown in Fig. 17. Kohler and his students repeated this synthesis and established the structure of the allenic acid by showing that it absorbed four atoms of hydrogen and that ozonization produced benzoylformic acid and phenyl α -naphthyl ketone. They were unable to resolve it, however; but the glycolic acid ester (Fig. 18) was prepared,



and fractional crystallization of the brucine salts effected a resolution of this molecule. Decomposition of the diastereoisomeric brucine salts gave the *d*- and *l*-forms of the acid, Fig. 18. The *d*-form melted at $145\text{--}146^\circ$ and had a specific rotation in ethyl acetate of $+29.5^\circ$. The *l*-form melted at $144\text{--}146^\circ$ and had a rotation of -28.4° . An equimolar mixture of *d*- and *l*-forms produced a racemic compound melting at 195° which was identical with the original racemic modification of Fig. 18. Hydrolysis of the active form of the compound shown in Fig. 18 yielded an active compound corresponding to Fig. 17 which was not isolated in crystalline form but which gave optically active crystalline esters.⁷ These investigations by Kohler leave no doubt as to the correctness of van't

⁵ Kohler, Walker, and Tishler, *J. Am. Chem. Soc.*, **57**, 1743 (1935).

⁶ Lapworth and Wechsler, *J. Chem. Soc.*, **97**, 38 (1910).

⁷ Kohler and Whiteher, *J. Am. Chem. Soc.*, **62**, 1489 (1940).

Hoff's prediction and constitute further evidence in favor of the tetrahedral carbon atom.

Molecules not far different from allenes in their general structure may be illustrated by 4-methylcyclohexylidenecacetic acid (Fig. 19), which

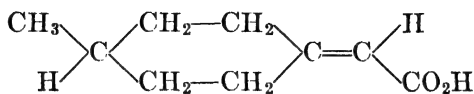


FIG. 19

was resolved by Pope, Perkin, and Wallach ⁸ in 1909. In this molecule one of the double bonds of the allene structure has been replaced by a six-membered ring. The methyl and hydrogen on carbon atom 4 lie in a plane perpendicular to the plane containing the carboxyl group and adjacent hydrogen (Fig. 20). The molecule has none of the elements of symmetry, and its mirror image is non-superimposable.

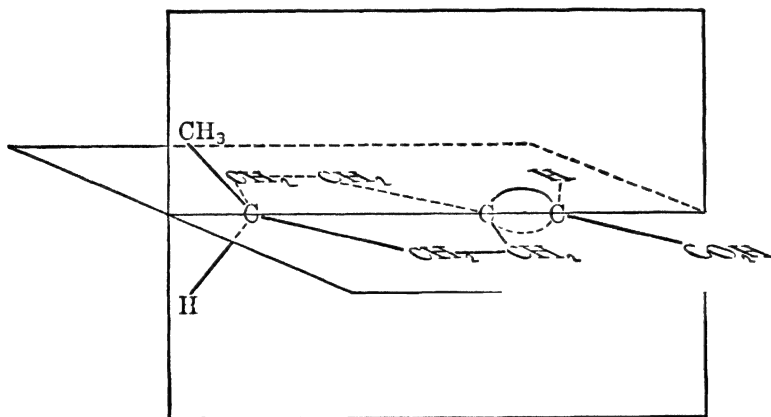


FIG. 20

Spiranes. If both double bonds of an allene are replaced by rings, spiranes result (Figs. 21, 22, 23, and 24). Construction of the models of these molecules shows that the planes of the rings are perpendicular to each other. In 1902 Aschan ⁹ pointed out that properly substituted

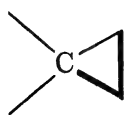


FIG. 21

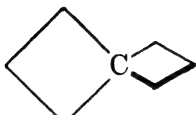


FIG. 22

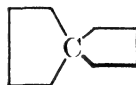


FIG. 23

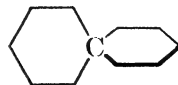


FIG. 24

⁸ Pope, Perkin, and Wallach, *Ann.*, **371**, 180 (1909); *J. Chem. Soc.*, **95**, 1789 (1909); Perkin and Pope, *ibid.*, **99**, 1510 (1911).

⁹ Aschan, *Ber.*, **35**, 3389 (1902).

spiranes are asymmetric molecules and hence should be capable of resolution.

No optically active forms of substituted spirocyclopentanes (Fig. 21) are known. The substituted spirocycloheptane shown in Fig. 25 was



FIG. 25

resolved in 1932 by Jansen and Pope¹⁰ by means of *d*- and *l*-camphor-10-sulfonic acids.

The dilactone, Fig. 26, was resolved by Mills and Nodder¹¹ in 1920.

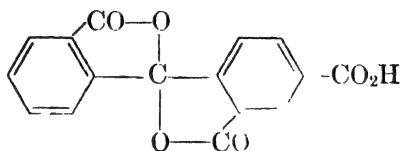


FIG. 26

Shortly afterwards Leuchs¹² resolved *bis*-dihydrocarbostyryl-3,3'-spirane-6,6'-disulfonic acid (Fig. 27) by means of quinine. Radulescu¹³ resolved the related spirane, Fig. 28.

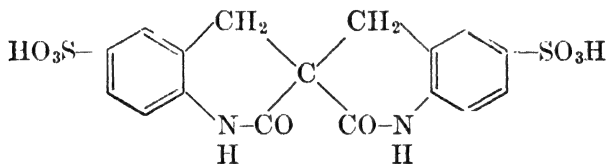


FIG. 27

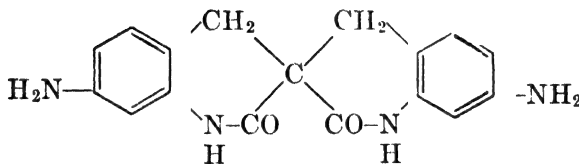


FIG. 28

Böeseken¹⁴ obtained evidence indicating the probability of optically

¹⁰ Jansen and Pope, *Chemistry & Industry*, **51**, 316 (1932).

¹¹ Mills and Nodder, *J. Chem. Soc.*, **117**, 1407 (1920).

¹² Leuchs, Conrad, and v. Katinsky, *Ber.*, **55**, 2131 (1922).

¹³ Radulescu, *Bul. soc. Stiinta Cluj*, **1**, 306 (1922); [*Chem. Zentr.*, (II), 139 (1923)].

¹⁴ Böeseken and Felix, *Ber.*, **61**, 1855 (1928).

active forms of the spirane (Fig. 29) produced by condensation of pentaerythritol with pyruvic acid.

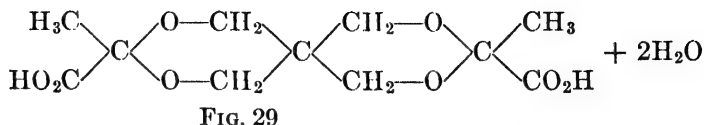


FIG. 29

Gibson and Levin¹⁵ recently resolved the closely related spirane shown in Fig. 30.

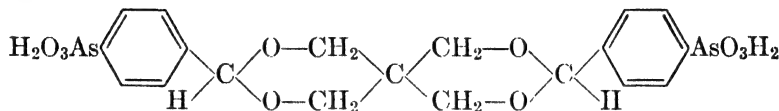


FIG. 30

In all the spiranes thus far discussed only one racemic modification is possible. The general formulas for the optical isomers of such compounds may be represented by Figs. 31 and 32.

If other asymmetric atoms are present then the number of isomers is increased. Thus, in the compound shown in Fig. 33 there are two asymmetric carbon atoms (marked *) in addition to the spirane atom.

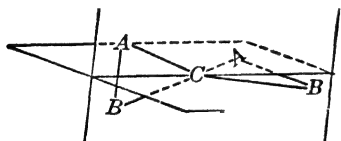


FIG. 31

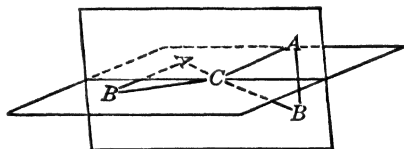


FIG. 32

dl-Modification

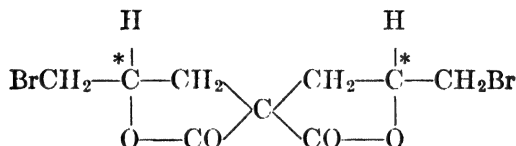


FIG. 33

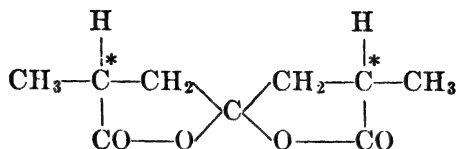
Such a molecule may exist in six optically active forms which constitute three racemic modifications. Leuchs¹⁶ actually obtained three racemic forms of the compound of Fig. 33. Sutter and Wijkman¹⁷

¹⁵ Gibson and Levin, *Proc. Roy. Soc. (London)*, **A141**, 494 (1933).

¹⁶ Leuchs, *Ber.*, **55**, 2131 (1922).

¹⁷ Sutter and Wijkman, *Ann.*, **519**, 97 (1935).

also prepared the three racemic modifications of the dilactone, Fig. 34.



Substituted Biphenyls and Other Compounds Exhibiting Restricted Rotation. A fourth general type of molecules containing no individual asymmetric atoms consists of certain substituted biphenyls and related compounds. Since this field is so extensive and since it involves the new concept of restricted rotation, Part VIII of this chapter is devoted to a detailed discussion of this type of isomerism.

PART VIII. ASYMMETRIC MOLECULES WITH RESTRICTED ROTATION ABOUT SINGLE BONDS

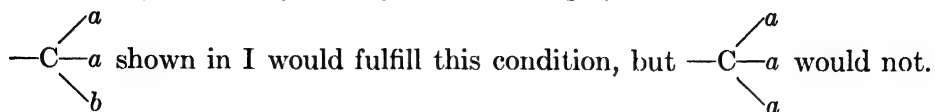
Introduction

Examination of the models of the three types of asymmetric molecules containing no individual asymmetric atoms (inositol, spiranes, and allenes, p. 336 ff.) shows that these molecules owe their asymmetry fundamentally to the concept of the tetrahedral carbon atom. However, a fourth group of such asymmetric molecules is known, the structure of which is characterized by an additional concept, that of restricted rotation about a single bond. This new concept of restricted rotation, together with a few additional principles, constitutes the fundamental basis for the stereoisomerism of the derivatives of biphenyl and their analogs.

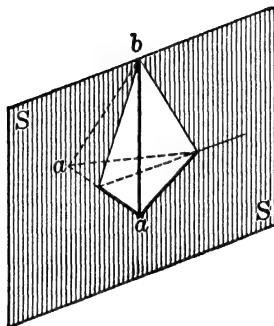
Fundamental Assumptions

In a general consideration of asymmetric molecules with restricted rotation about a single bond, the structural factors involved may best be understood by selecting two univalent radicals $R-$ and $R'-$ which may be the same or different. Each of these must possess a plane of symmetry, denoted by S and S' , which obviously must include the free valences, denoted by P and P' . A plane of symmetry is a necessity in the radicals so that asymmetry in the molecule produced by combining the two radicals cannot be assigned to the particular structure of any component part of the molecule. Such radicals, moreover, must possess

only *one* plane of symmetry. For example, the tetrahedral radical

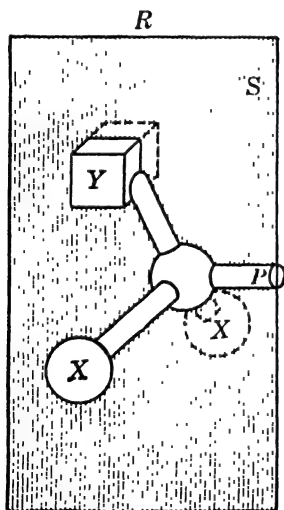


The latter has three planes of symmetry each drawn through the free

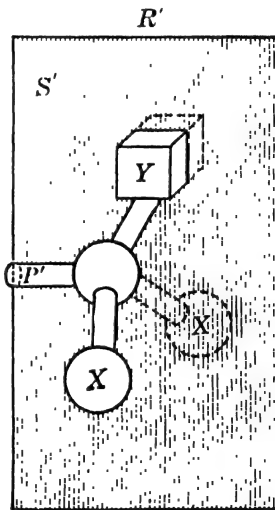


I

valence and one of the *a*'s. Provided that the single plane of symmetry is assumed, the radicals may possess any kind of geometric structure, and these may be illustrated by specific examples in II and III. If these



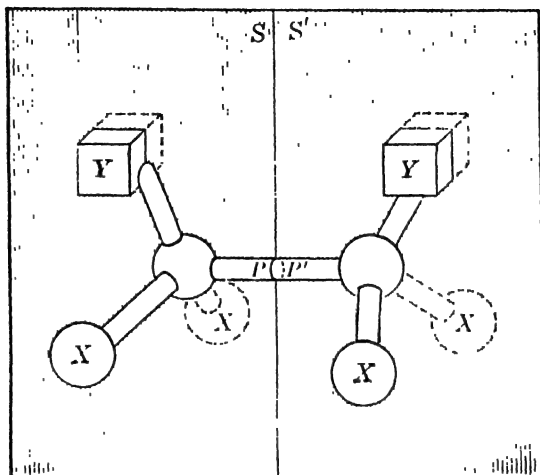
II



III

two radicals are joined by their free valences, a "pivot bond" between them is formed (IV) and the two atoms to which the pivot bond is attached may be called pivot atoms. Assuming that this union occurs without distortion of the radicals, the pivot bond lies in both planes *S* and *S'* regardless of their positions relative to each other. If the radicals

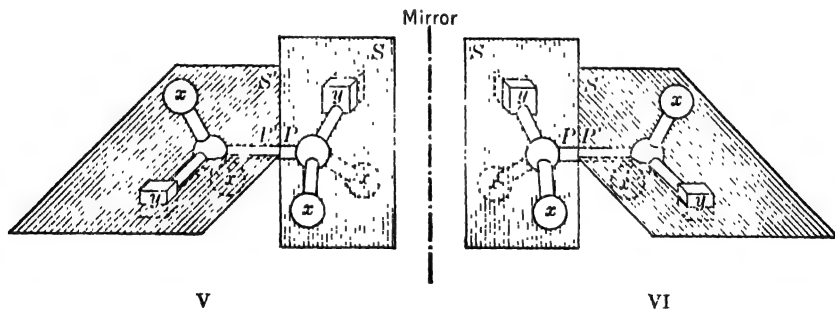
are free to rotate about the pivot bond, the planes S and S' at some phase in the rotation become coplanar as shown in IV. Hence the molecule



IV

has a plane of symmetry and therefore cannot exist in enantiomorphic forms.

On the other hand, if free rotation of the radicals about the pivot bond is restricted so that S and S' cannot become coplanar, then a structure such as that shown in V results. The plane S may be assumed to be in the plane of the paper and S' at any angle to the paper. A molecule with this structure, owing to the restricted rotation about the



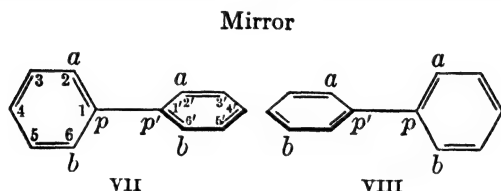
V

VI

pivot bond, has none of the elements of symmetry and hence its mirror image shown in VI is not identical with it. A careful scrutiny of V and VI indicates that these mirror images cannot be made to coincide with each other. This general concept of the existence of enantiomorphic forms emphasizes the two essential prerequisites for observance of optical isomerism in compounds of this type: (1) restricted rotation of the planes of symmetry of the radicals about the pivot bond; (2) each of the

radicals united by the pivot bond has one and only one plane of symmetry. In molecules in which there are no sources of dissymmetry besides the pivot bond with restricted rotation, the only form of stereoisomerism which can occur is enantiomorphism.

The general statement assumes no particular structure for R— or R'—, nor does it refer the hindrance of rotation to any particular cause. It admits, however, as a special case, molecules such as biphenyls and their analogs in which *P* and *P'* are free valences attached to rather rigidly constructed planar rings. Thus, a substituted biphenyl of this type is shown in VII and VIII. The rotation about the pivot bond



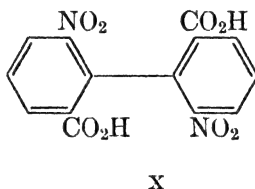
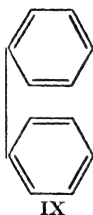
connecting the pivot or 1,1' carbon atoms is restricted by the presence of the *a* and *b* groups in the *ortho* positions. The presence of the *a* and *b* groups in each ring eliminates all planes of symmetry in each component radical except that which extends through the plane of the ring in which *a*, *b*, and the pivot bond lie.

The generalized form of theory just given does not attempt to fix the cause which accounts for the restricted rotation. Nevertheless, in every case of isomerism of this type now known, the experimental data are consistent with the assumption that the restriction of rotation is due to interference between atoms or groups in close proximity to the pivot bond or bonds. Thus, in application to date the "restricted rotation" theory coincides with a more specialized "interference theory" which not only assumes restricted rotation but assigns mechanical or other interference between portions of the molecule as the cause of restriction. This "interference theory" postulates a new variety of steric hindrance. The history of the new doctrine, however, has been widely different from that of the old theory of steric hindrance. The main distinction between the two is that the new theory leads directly to predictions as to the number of isomers to be expected in given cases, whereas the old one could be applied only to dynamic phenomena such as rates of reaction.

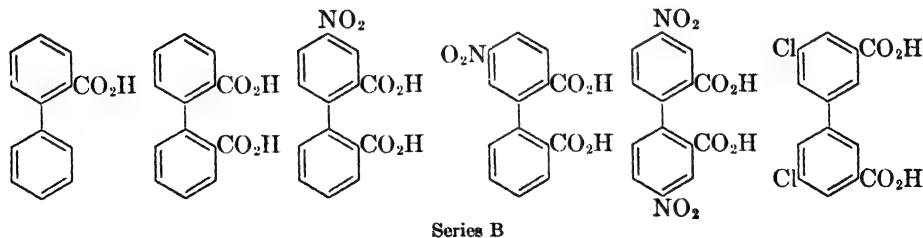
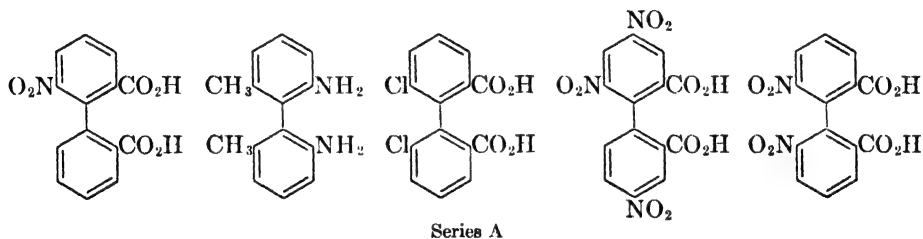
Wherever restricted rotation is due to such interference it is obvious that, in such molecules, the R and R' groups which are joined to form the molecule might equally well be asymmetric. Under these conditions, the restriction of rotation introduces a new center of asymmetry and thus makes theoretically possible additional stereoisomers over and above those present if free rotation is assumed.

Introduction to Optical Isomerism of Biphenyls ¹

The discovery of optical activity among biphenyl derivatives was due to a curious sequence of events arising out of Kaufler's attempt to explain the fact that benzidine exhibited certain properties which did not appear normal for a bicyclic molecule with coplanar rings. In 1907 ² he proposed for biphenyl derivatives the folded structure represented by IX. Extensive investigation during the succeeding fifteen years tended to support such an hypothesis, but much of the experimental work was later shown to be erroneous. Subsequent studies of biphenyls entirely disproved the folded structure. It was during a research on this problem that Christie and Kenner, ³ in 1922, successfully resolved one of the dinitrodiphenic acids (X). These experimental results remained



unchallenged and led to attempts in many different laboratories to resolve various biphenyl derivatives. It speedily became evident that some of them, such as those in Series A, could easily be resolved, whereas others, such as those in Series B, resisted all attempts at resolution.



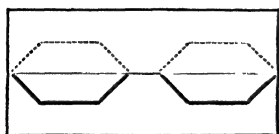
¹ Adams and Yuan, *Chem. Rev.*, **12**, 262 (1933); Hillemann, *Angew. Chem.*, **50**, 435 (1937.)

² Kaufler, *Ann.*, **351**, 151 (1907); *Ber.*, **40**, 3250 (1907).

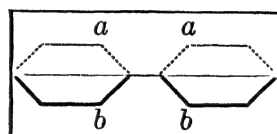
³ Christie and Kenner, *J. Chem. Soc.*, **121**, 614 (1922).

Experimental evidence favors a planar structure for a phenyl or substituted phenyl group. In biphenyl, it is commonly assumed that the two planar rings are coaxial. The term "coaxial" means that the pivot bond, when extended, passes through the two carbon atoms *para* to the pivot atoms. The diagrams for biphenyls are drawn in conformity with this assumption, but it must be remembered that this convention is purely arbitrary.

If the two rings in biphenyl itself are thought of as coaxial and coplanar, the molecule has a plane of symmetry (in which the pivot bond lies) perpendicular to the common plane of the two rings XI. In a compound of the type XII, however, the substituents are so distributed that

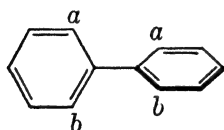


XI

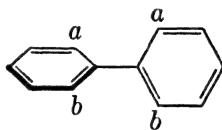


XII

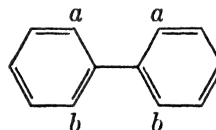
no plane of symmetry exists vertical to the rings; in other words, the reflection symmetry of each of the two rings with respect to this plane is destroyed. As Christie and Kenner³ pointed out, if such a molecule as XII is twisted so that the rings, though remaining coaxial, are no longer coplanar, the molecule assumes a dissymmetric configuration and makes enantiomorphic forms (XIII) and (XIV) possible.



XIII



XIV



XV

Provided that the rings could be held permanently in the positions indicated in XIII and XIV, the enantiomorphic forms would be stable and the racemic modification of such a molecule could be resolved. This pertinent suggestion is not sufficient, however, for it at once raises the question of free rotation about the pivot bond joining the two rings. The dissymmetry in the coaxial-noncoplanar phases of the substances (XIII) and (XIV) would be destroyed during the course of free rotation, for in the coplanar phase (XV) the molecule contains a plane of symmetry—the common plane of the two rings. That is to say, free rotation would cause a very rapid autoracemization of the optically active compounds XIII and XIV. In fact, it would effectively prevent resolution. Hence, if the rings of such molecules as those under consideration are supposed to be coaxial but permanently noncoplanar, there must be some

adequate cause to prevent the free rotation postulated by the classic theory.

A probable source of this hindrance to free rotation was pointed out almost simultaneously by Turner and Le Fèvre,⁴ Bell and Kenyon,⁵ and Mills.⁶ The hypothesis advanced in slightly different forms is that the effective size of these *ortho* substituents conditions the occurrence of optical activity in biphenyl derivatives—provided that on each ring the substituents are introduced in such fashion as to leave the ring with no vertical plane of symmetry. If the *ortho* substituents are sufficiently large, they interfere with one another in the coplanar position, either by the mechanical or repulsive action of their fields of force. Only in the noncoplanar positions is there room enough for all of them. Therefore, complete rotation is prevented and optical resolution becomes possible.

One immediately obvious merit of the theory is that it indicates a reason why the biphenyls mentioned in Series A, which have at least three non-hydrogen substituents in the four positions *ortho* to the pivot bond, have been obtained optically active, whereas those in Series B with two or less such substituents could not be resolved. Two *ortho* substituents in one ring hinder the *ortho* substituent or substituents in the second ring from passing, and hence prevent the two rings from becoming coplanar. No one of the compounds in Series B is so constructed, although in most of them each ring has no vertical plane of symmetry and only a single plane of symmetry coincident with the plane of the rings.

In discussing the extensive results in the field of biphenyls and related compounds on the basis of this interference theory as a working hypothesis, certain of its consequences may be deduced. The deductions will be grouped under two heads: (A) those which apply to molecules containing only one pivot bond with restricted rotation, and (B) those which apply to molecules containing more than one pivot bond with restricted rotation.

(A) Compounds Containing Only One Pivot Bond with Restricted Rotation. There is no reason why the phenomena observed in the earliest instances should be confined to simple derivatives of biphenyl. Substituted binaphthyls, bipyrryls, bipyridyls, as well as mixed compounds like phenylnaphthalenes and phenylpyridines, should act in similar fashion. Indeed, there is no reason why either of the pivot atoms must be a ring member if the conditions for dissymmetry and interference are fulfilled. Compounds have already been prepared where only one of the

⁴ Turner and Le Fèvre, *Chemistry & Industry*, **45**, 831, 883 (1926).

⁵ Bell and Kenyon, *ibid.*, **45**, 864 (1926).

⁶ Mills, *ibid.*, **45**, 884, 905 (1926).

pivot atoms is a ring member, but none has as yet been synthesized in which both pivot atoms are in non-ring structures.

In the earlier experiments on derivatives of biphenyl it was assumed that a given number of substituents *ortho* to the pivot atoms must be other than hydrogen, but the fundamental hypothesis does not demand this. Optically active compounds in the bicyclic series containing 4, 3, 2, or 1 non-hydrogen substituents in the four positions *ortho* to the pivot bond have been obtained. In fact, a hypothetical optically active molecule with no *ortho* non-hydrogen substituents can be written and will be discussed in the latter part of the section.

The occurrence of enantiomorphism in biphenyls depends upon the specific properties of the univalent substituents present. If these substituents are designated by *a*, *b*, etc., it is impossible to determine by inspection of the type structural formula whether the substance exists in enantiomorphic forms.

In the biphenyl and closely related series, when the dissymmetry conditions have been met, the occurrence of enantiomorphism would be expected to depend upon (a) the size of the *ortho* substituents; (b) the effect of the various influences on the length of the pivot bond and the rigidity of the *ortho* substituents. Temperature and solvent would be expected to play a role. Furthermore, substituents other than *ortho* might modify the relations of the groups to one another around the pivot bond.

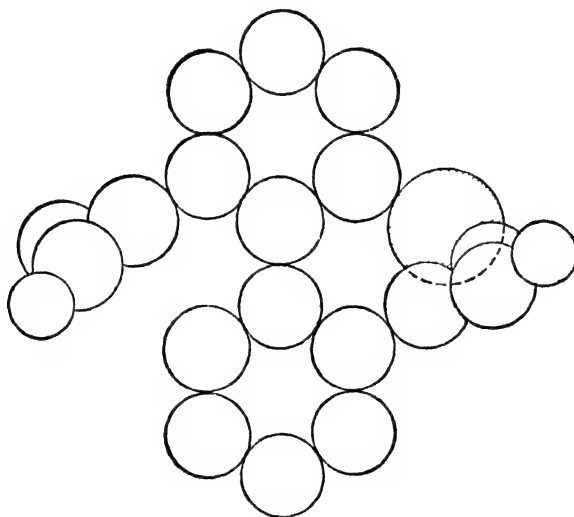
(B) Compounds Containing More Than One Pivot Bond with Restricted Rotation. Considerations analogous to those discussed under (A) hold here. Compounds such as dipyrnyl benzenes, for example, should act much like diphenyl benzenes. The dissymmetry and interference conditions are the only ones necessary for the occurrence of stereoisomeric forms. Molecules with proper *ortho* substituents have been obtained in the expected number of isomers, but it is possible to formulate compounds which should exist in stereoisomeric forms though no *ortho* substituents are present.

With two pivot bonds and restricted rotation, various forms of stereoisomerism can occur. Optically inactive *meso* forms, pairs of optically inactive diastereoisomers (*cis* and *trans*) may result if the univalent substituents are properly distributed over the molecular skeleton.

All forms of stereoisomerism among these compounds depend upon the specific properties of the univalent substituents and cannot be inferred by consideration of the type structural formula alone; they depend on the same specific influences (size of substituents, temperature, solvent, etc.) which condition the occurrence of enantiomorphism in compounds containing only one pivot bond with restricted rotation.

X-Ray Data

Mills,⁶ in proposing the purely mechanical idea of steric hindrance between the *ortho* substituents in the substituted biphenyls so as to restrict rotation, built up a model from atoms drawn to scale. He was thus able to demonstrate that two bulky *ortho* substituents in the one ring would interfere with the free rotation of the second ring, owing to collisions between them and the third *ortho* substituent. For example, in 2-chloro-6,6'-dicarboxybiphenyl (XVI) the carboxyl group attached to



XVI

the lower nucleus can pass neither the chlorine atom (large shaded circle) nor the other carboxyl group, and hence is confined to a limited region in front of the plane of the upper ring. On the other hand, if two of the groups are small, free rotation is possible. This is in accord with the facts in the case of diphenic acid and its derivatives in which the remaining two *ortho* hydrogens are unsubstituted, for in these compounds the two *ortho* hydrogen atoms are not bulky enough to prevent the free rotation of the two rings about their common axis.

The further application to the biphenyl problem of values of atomic size, obtained by physical measurements, was a natural development. Atomic dimensions inferred from x-ray data were used to demonstrate the probability of collision between the amino and methyl groups in 2,2'-dimethyl-6,6'-diaminobiphenyl.⁷

⁷ Meisenheimer and Höring, *Ber.*, **60**, 1425 (1927).

Methods have been suggested which permit definite predictions concerning the resolvability of any given biphenyl. Stanley and Adams⁸ called the difference between the sum of the internuclear distances * of the 2,2'-substituents and the distance between the 2,2' ring carbon atoms⁹ (2.90 Å) the "interference value" and demonstrated that this value measured the relative degree of interference that might be expected in the molecule. Where the interference value was negative, the compound could not be resolved; where positive, it could be resolved. Molecules with only a slight positive interference value racemized readily. The estimated interferences paralleled to a surprising degree the relative racemization rates of 2,2',6,6'-tetrasubstituted biphenyls as found experimentally but did not conform to the results obtained in the study of 2,2',6-tri- or 2,2'-disubstituted compounds. The method is purely empirical.

The building of models for the biphenyls¹⁰ in which the atoms are drawn to scale as spheres and then predicting the interference of the 2,2'-substituents has been a common procedure. It is uniformly satisfactory only for the 2,2',6,6'-tetrasubstituted biphenyls. It involves arbitrary assumptions as to the effective diameter of various atoms (i.e., as to how close atoms can approach without interfering), and thus like the previous approach to the prediction of resolvability must be considered empirical.

Experimental Evidence for the Coaxial-Noncoplanar Model

The concept of the coaxial-noncoplanar configuration and the theory of restricted rotation are more or less inseparable. Actually the former is much more fundamental and the latter supplementary. Experiments which may verify the restricted rotation theory incidentally will prove the noncoplanar configuration. On the other hand, those investigations which offer merely additional evidence in favor of the noncoplanar model may advantageously be considered separately for the clarity of presentation.

The biphenyl molecules with three or four substituents in the 2,2',6,6'-positions which have been resolved are now well over fifty in

⁸ Stanley and Adams, *J. Am. Chem. Soc.*, **52**, 1200 (1930).

* The "internuclear distance" refers to the distance, as determined by x-rays and adjusted for aromatic compounds, from the ring carbon atom to the substituent group, Cl, NO₂, CH₃, etc. Where the substituent has atoms or groups attached to it, as the NO₂ or CH₃, allowance was made for the additional effect of such atoms or groups.

⁹ Dhar, *Indian J. Phys.*, **7**, 43 (1932).

¹⁰ Lesslie and Turner, *J. Chem. Soc.*, 2021 (1932).

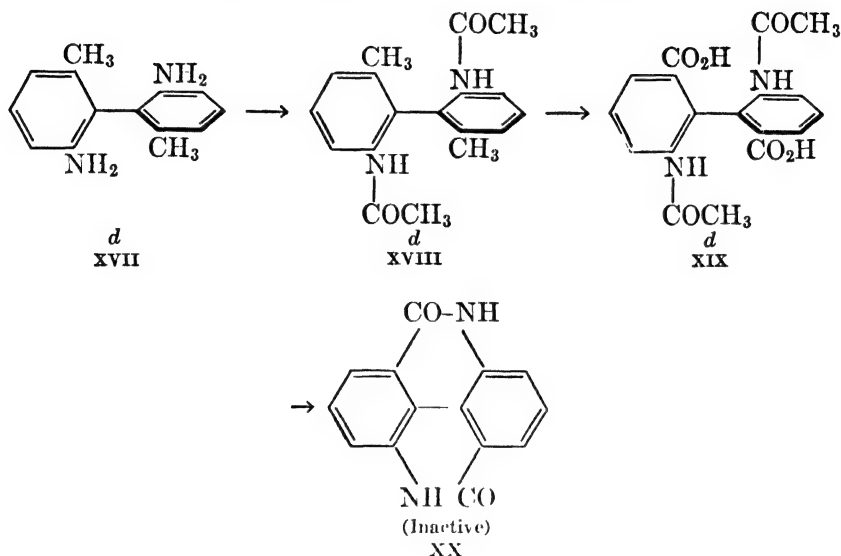
number and represent a wide variety of types. A description of these may be found in the original publications.^{3,7,11-45}

A natural extension of the study has been made into fused ring systems. If the coaxial-noncoplanar view is correct, properly substituted binaphthyls, bianthranyl, and molecules of a similar nature should show optical isomerism. Many such compounds have been resolved.⁴⁶⁻⁵²

Elimination of Optical Activity through 2,2'-Ring Closure. One of the most interesting and convincing pieces of evidence demonstrating the noncoplanar structure for substituted biphenyls was found by a study of certain 2,2',6,6'-substituted biphenyls which contain groupings

- ¹¹ Christie and Kenner, *J. Chem. Soc.*, 470 (1926).
- ¹² Sako, *Bull. Chem. Soc. Japan*, **9**, 393 (1934).
- ¹³ Christie, James, and Kenner, *J. Chem. Soc.*, **123**, 1948 (1923).
- ¹⁴ Yuan and Hsu, *J. Chinese Chem. Soc.*, **3**, 206 (1935).
- ¹⁵ Kenner and Turner, *J. Chem. Soc.*, 2340 (1928).
- ¹⁶ Stanley, McMahon, and Adams, *J. Am. Chem. Soc.*, **55**, 706 (1933).
- ¹⁷ Kenner, *Chemistry & Industry*, **46**, 219 (1927).
- ¹⁸ Li, Doctoral Dissertation, University of Illinois, 1934.
- ¹⁹ Mascarelli, *Atti accad. Lincei*, **6**, 60 (1927).
- ²⁰ Sako, *Mem. Coll. Eng. Kyushu Imp. Univ.*, **6**, 263 (1932).
- ²¹ Kleiderer and Adams, *J. Am. Chem. Soc.*, **53**, 1575 (1931).
- ²² Kleiderer and Adams, *ibid.*, **55**, 716 (1933).
- ²³ Angeletti and Guala, *Gazz. chim. ital.*, **61**, 651 (1931).
- ²⁴ Angeletti, *ibid.*, **62**, 376 (1932).
- ²⁵ Angeletti, *ibid.*, **65**, 819 (1935).
- ²⁶ Angeletti, *ibid.*, **63**, 145 (1933).
- ²⁷ Bell, *J. Chem. Soc.*, 835 (1934).
- ²⁸ Van Arendonk, Becker, and Adams, *J. Am. Chem. Soc.*, **55**, 4230 (1933).
- ²⁹ Hsing and Adams, *ibid.*, **58**, 587 (1936).
- ³⁰ Moyer and Adams, *ibid.*, **51**, 630 (1929).
- ³¹ Knauf and Adams, *ibid.*, **55**, 4704 (1933).
- ³² Bock, Moyer, and Adams, *ibid.*, **52**, 2054 (1930).
- ³³ White and Adams, *ibid.*, **54**, 2104 (1932).
- ³⁴ Bell and Robinson, *J. Chem. Soc.*, 1695 (1927).
- ³⁵ Christie and Kenner, *ibid.*, **123**, 779 (1923).
- ³⁶ Christie, Holderness, and Kenner, *ibid.*, 671 (1926).
- ³⁷ Stearns and Adams, *J. Am. Chem. Soc.*, **52**, 2070 (1930).
- ³⁸ Lesslie and Turner, *J. Chem. Soc.*, 1758 (1930).
- ³⁹ Stoughton and Adams, *J. Am. Chem. Soc.*, **52**, 5263 (1930).
- ⁴⁰ Adams and Hale, *ibid.*, **61**, 2825 (1939).
- ⁴¹ Stoughton and Adams, *ibid.*, **54**, 4426 (1932).
- ⁴² Chien and Adams, *ibid.*, **56**, 1787 (1934).
- ⁴³ Hanford and Adams, *ibid.*, **57**, 1592 (1935).
- ⁴⁴ Yuan and Adams, *ibid.*, **54**, 4434 (1932).
- ⁴⁵ Li and Adams, *ibid.*, **57**, 1565 (1935).
- ⁴⁶ Kuhn and Goldfinger, *Ann.*, **470**, 183 (1929); Wittig and Petri, *Ann.*, **505**, 25 (1933).
- ⁴⁷ Kuhn and Albrecht, *Ann.*, **465**, 282 (1928).
- ⁴⁸ Stanley and Adams, *Rec. trav. chim.*, **48**, 1035 (1929).
- ⁴⁹ Murahashi, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **17**, 297 (1932).
- ⁵⁰ Ioffe and Grachev, *J. Gen. Chem. (U.S.S.R.)*, **5**, 950 (1935).
- ⁵¹ Kuhn and Albrecht, *Ann.*, **464**, 91 (1928).
- ⁵² Wallis and Moyer, *J. Am. Chem. Soc.*, **55**, 2598 (1933).

capable of producing rings through the 2,2'-positions. When 2,2'-dimethyl-6,6'-diaminobiphenyl ⁷ (XVII) is acetylated, the introduction of acetyl groups does not effect any noticeable racemization. The diacetyl compound (XVIII), in turn, is oxidized to the dicarboxylic acid (XIX) which is still optically active, but when the latter is hydrolyzed by cold acid, an inactive dilactam (XX) is obtained.



The same phenomenon was noticed in 2-nitro-6,6'-dicarboxybiphenyl, the *d*-form of which produces the corresponding optically inactive fluorenone when it is warmed with sulfuric acid. The fluorenone could not be resolved.^{53, 54, 55} Similar observations^{46, 47} were made on other compounds in which a five- or six-membered ring linked the 2- and 2'-positions.

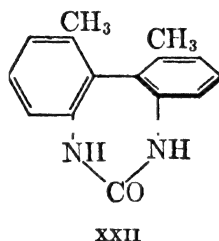
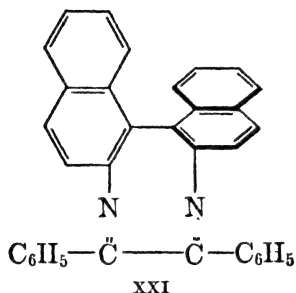
The disappearance of optical activity cannot be attributed to racemization, since the optical isomers are stable under the conditions of ring closure. Before the 2- and 2'-positions are linked in a ring the molecule has the coaxial-noncoplanar configuration. On the basis of the present knowledge of the stereochemistry of ring compounds, five- or six-membered rings joining the two benzene rings of a biphenyl nucleus through *ortho* positions are planar. As soon as the 2- and 2'-carbons are linked by such a ring system, the two halves of the molecule are forced into a coplanar configuration. Thus a plane of symmetry is introduced into the molecule and optical activity disappears.

⁵³ Bell and Robinson, *J. Chem. Soc.*, 2234 (1927).

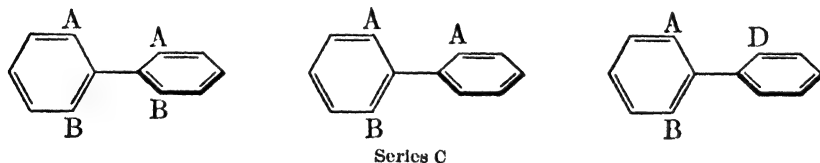
⁵⁴ Kuhn and Jacob, *Ber.*, **58**, 1432 (1925).

⁵⁵ Underwood and Kochmann, *J. Am. Chem. Soc.*, **46**, 2069 (1924).

It is accepted that rings larger than six-membered are ordinarily strainless and nonplanar. If the 2- and 2'-positions in a resolvable biphenyl derivative are linked therefore in a strainless ring, the two nuclei of the molecule can still be noncoplanar and the potential optical activity can remain. This was demonstrated by the condensation of *d*-2,2'-diamino-1,1'-binaphthyl with benzil;^{46, 56} the product was highly active (XXI). In this case the 2,2'-carbons are in an eight-membered ring. Several analogous optically active molecules containing seven-membered rings have been described,^{56, 57} of which one is shown in formula XXII.



Unsymmetrical Substitution in Each Ring. It is implied in the coaxial-noncoplanar model of a biphenyl that each ring in itself must be unsymmetrically substituted in order that no vertical plane of symmetry may exist and the compound may therefore be resolvable. When the coaxial-noncoplanar theory was first suggested, the active compounds known at that time, and even those prepared directly afterward, contained different groups in the 2,2'- or 6,6'-positions. They are represented by examples in Series C.



However, a phenyl group can be unsymmetrically substituted in several ways.^{58, 59} All the 2,2',6,6'-positions may be occupied by identical atoms or groups, provided that substituents *meta* to the linkage of the two rings make each ring unsymmetrical. Formulas in Series D

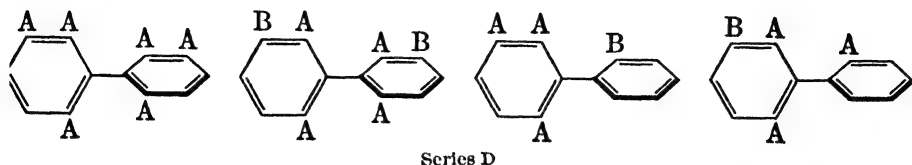
⁵⁶ Täuber, *Ber.*, **25**, 3287 (1892); **26**, 1703 (1893).

⁵⁷ Wittig and Petri, *Ann.*, **505**, 25 (1933).

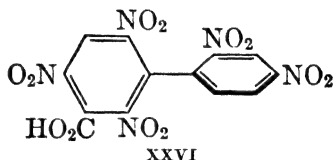
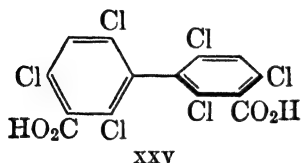
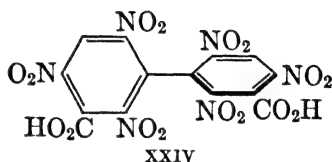
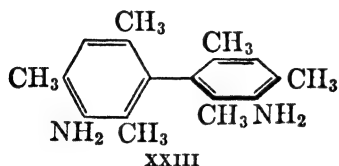
⁵⁸ Mascarelli, *Gazz. chim. ital.*, **58**, 791, 865 (1928).

⁵⁹ Hyde and Adams, *J. Am. Chem. Soc.*, **50**, 2499 (1928).

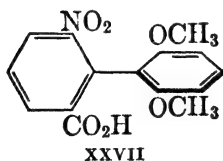
represent a few of the possibilities in molecules containing at least two identical *ortho* substituents in the same ring.



A number of these have been prepared and resolved^{80, 32, 33, 37} (XXIII, XXIV, XXV, XXVI). All the active forms are exceedingly stable.



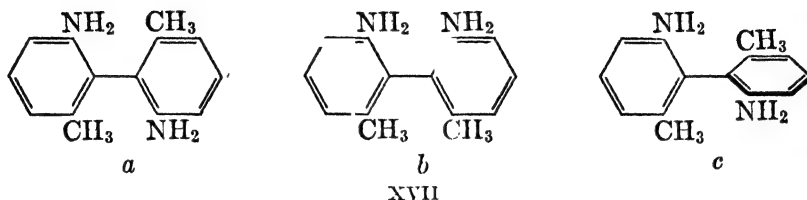
The general idea of a coaxial-noncoplanar structure for substituted biphenyls, with the supplementary assumption of no vertical plane of symmetry in each ring, was quickly and generally adopted. The fact that compound XXVII could not be resolved demonstrates that a symmetrically substituted biphenyl is not capable of resolution even though *ortho* groups of the proper character may be present²⁸ (see also p. 371).



Physical Data. Certain physical data have appeared which support the noncoplanar concept. From an x-ray study⁶⁰ the conclusion was drawn that, in certain 2,2',6,6'-derivatives of biphenyl, the two rings are in planes turned from each other at an angle not greater than 45°, while the rings in biphenyl itself are coplanar. Dipole measure-

⁶⁰ Clark and Pickett, *ibid.*, **53**, 167 (1931); Pickett, *Nature*, **131**, 515 (1933); *Proc Roy. Soc. (London)*, **142A**, 333 (1933).

ments⁶¹ upon optically active 2,2'-diamino-6,6'-dimethylbiphenyl (XVII) have led to pertinent results. Of the three possible formulas given below, XVIIa, which is coplanar, should give no moment, while XVIIb, also coplanar, gives a calculated moment of 1.99×10^{-18} . The value actually found was 1.66×10^{-18} , thus offering evidence for formula XVIIc. It may be calculated from these measurements that the angle of the two planes in this molecule is 67° .



Absorption spectra measurements on various biphenyls⁶² have shown that compounds with established restricted rotation exhibit a marked decrease in the characteristic absorption compared with similar compounds where this restriction is not present. This decrease is attributed to the prevention of conjugation between the two rings due to the non-coplanar configuration of the rings caused by the restriction of rotation.

A study of resonance energies of several biphenyl derivatives also indicates that the rings are not coplanar.⁶³

The comparative stability of the more easily racemized biphenyls has been determined generally by means of half-life periods. The decrease in optical activity obeys the law of a reversible first-order reaction,⁶⁴ and the rate of racemization may be expressed in terms of half-life periods. A kinetic study of the racemization of 2,2'-diamino-6,6'-dimethylbiphenyl⁶⁵ has confirmed that in this case at least the racemization both in the gaseous phase and in solution is homogeneous and unimolecular. The activation energy was determined and it was concluded that approximately 22.5 kcal. is necessary to bend the bonds and overcome the repulsion to such an extent that the planar model is possible. It was deduced also that any biphenyl compounds possessing an activation energy for racemization less than about 20.0 kcal. would racemize too rapidly to be resolved.

The activation energies of a variety of optically active biphenyls⁶⁶

⁶¹ Bergmann and Engel, *Z. physik. Chem.*, **15B**, 85 (1931).

⁶² Pickett, Walter, and France, *J. Am. Chem. Soc.*, **58**, 2296 (1936); Pickett, *ibid.*, **58**, 2299 (1936); O'Shaughnessy and Rodebush, *ibid.*, **62**, 2906 (1940).

⁶³ Brüll, *Gazz. chim. ital.*, **65**, 28 (1935).

⁶⁴ Kuhn and Albrecht, *Ann.*, **455**, 272 (1927); **458**, 221 (1927); Smith, *J. Am. Chem. Soc.*, **49**, 43 (1927).

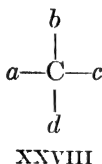
⁶⁵ Kistiakowsky and Smith, *J. Am. Chem. Soc.*, **58**, 1043 (1936).

⁶⁶ Li and Adams, *ibid.*, **57**, 1565 (1935).

with widely varying half-life periods have been determined. They all fall within 18.0 and 25.0 kcal. Since the activation energies cannot be determined with an experimental accuracy sufficient to allow this constant to be used for a comparison of the relative stabilities of such compounds, the half-life periods must be used for this purpose.⁶⁷

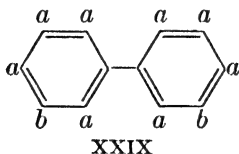
Characteristics of Biphenyl Isomerism

The peculiarity of the stereoisomerism in the biphenyl and related series should be explicitly pointed out. The theory of van't Hoff predicts that any compound of the type XXVIII should exist in two stereo-



isomeric forms—assuming that the substituents *a*, *b*, *c*, *d* are univalent radicals which are not in themselves optically active. It is the very essence of this theory that the existence of the two isomers is in no wise dependent upon the *specific* properties of the individual radicals, but is conditioned solely by the fact that *all four are different*. Like considerations hold when van't Hoff's idea is applied to compounds containing more than one asymmetric carbon atom; they are equally applicable to cyclic and to open-chain compounds; they account for the stereoisomerism in the allene and spirane series; and they apply also to molecular dissymmetry such as that observed among the inositols. Even the stereoisomerism attributed to elements other than carbon can be explained without change in this aspect of the van't Hoff theory.

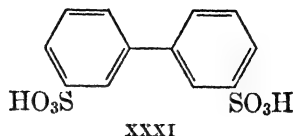
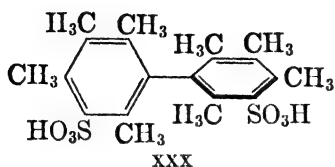
However, the stereoisomerism in the biphenyl and related series is not in accord with this widespread rule. A pair of substances has been prepared which illustrates perfectly the impossibility of predicting the number of stereoisomeric forms of the compound defined only by the type formula XXIX. The compound 2,2',4,4',5,5',6,6'-octamethyl-



3,3'-biphenyldisulfonic acid (XXX) was resolved into its optical antipodes

⁶⁷ Adams and Kornblum, *ibid.*, **63**, 188 (1941).

and the active forms cannot be racemized by any of the usual methods.³¹ On the other hand, attempts to resolve the corresponding biphenyl-3,3'-disulfonic acid (XXXI) were unavailing.



Thus, if *a* is the hydrogen atom in the general formula XXIX, there is one form; if *a* is the methyl radical there are two. In other words, the number of forms is not a type property of the molecule, but depends upon the specific nature of the univalent substituents. It is thus evident that no mere extension of the van't Hoff theory (such as the one introduced by Werner) can account for the stereoisomerism in the biphenyl and analogous series.

The discussion of biphenyls has been limited to those which are capable of resolution. It is important to recognize, however, that any biphenyls in which the *ortho* groups interfere with each other will have restricted rotation and a noncoplanar structure, even though they are non-resolvable on account of symmetrical substitution in the rings. They differ therefore from biphenyls in which no *ortho* groups are present or in which the *ortho* groups do not interfere, since the latter will have free rotation in the molecules.

Experimental Evidence Relative to the Size of the 2,2',6,6'-Groups

The preceding discussion has established satisfactorily the coaxial-noncoplanar structure of biphenyls which have certain substituents in the 2,2',6,6'-positions and are unsymmetrically substituted in each ring. More specific information in regard to the character of the 2,2',6,6'-atoms or groups and their relative effect upon the restriction of free rotation between the rings of the biphenyl molecule will now be considered.

Up to 1930 the antipodes of all the known *ortho*-tetrasubstituted resolvable biphenyls were found to be highly stable; they could not be racemized in boiling acid, alkaline, or neutral solution. On the other hand, the trisubstituted compounds³⁷ were found to racemize in boiling solutions. On the basis of the obstacle theory, the difference between these two classes of compounds is explicable.

The racemization of active biphenyl derivatives or mutarotation of their salts may be explained by the fact that thermal agitation causes

the groups in the 2,2',6,6'-positions to slip by each other. The nuclei to which they are attached are thus allowed to pass through the common plane, and one active form changes into the other.

The obstacle theory further leads to the prediction that, merely by modifying properly the size of the 2,2',6,6'-groups, optically active biphenyls with widely varying degrees of stability to racemization may be prepared. The study of the comparative rates of racemization of different active biphenyls offers a semi-quantitative approach to the determination of the importance of the size of the groups in relation to the blocking effect.

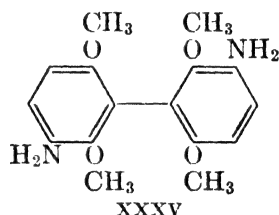
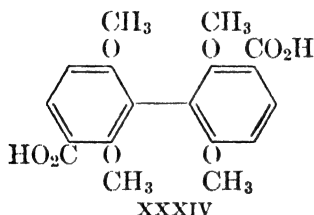
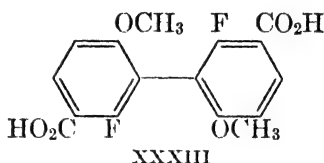
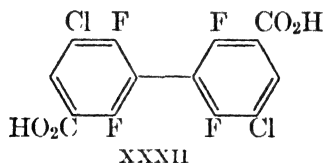
Several pertinent and interesting phases of this general problem have been studied experimentally: (a) The preparation of 2,2',6,6'-tetrasubstituted biphenyls which, unlike those at first studied, are non-resolvable; (b) the preparation of tetrasubstituted compounds which readily racemize and of trisubstituted compounds which are immune to racemization; (c) the comparison of groups by a study of the rates of racemization of a series of biphenyls in which two of three substituents or three of four substituents in the 2,2',6,6'-positions remain constant and the third or fourth is varied; (d) the observation of rotational changes during the replacement of one or two groups in the 2,2',6,6'-positions by other groups; (e) the preparation of active 2,2'-disubstituted and 2-monosubstituted biphenyls; (f) the effect on rates of racemization of a modification of the atoms or groups combined to the atoms attached to the ring in the 2,2',6,6'-positions; (g) the effect upon the stability of the active molecules of additional groups substituted in positions other than the 2,2',6,6'; (h) the comparison of biphenyls in which the identical triplets of groups in the *ortho* positions hold different relative positions to each other; (i) the comparison of the rate of racemization of active biphenyls and their salts.

These lines of research will be discussed in order. From the practical standpoint, the problem of studying the desired effects lies in the selection of the proper groups to substitute in the biphenyl and the preparation of such compounds. Evidence from many sources indicates the fluorine and hydroxyl or methoxyl to be among the smallest atoms or groups other than hydrogen; amino and carboxyl groups are not much larger.

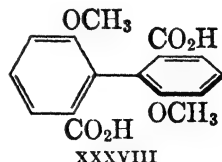
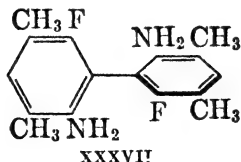
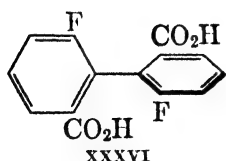
It is deserving of mention that, in the resolution of a biphenyl of which the optically active forms are very easily racemized, either a single diastereoisomeric salt is isolated or two diastereoisomeric salts, one of which is very readily converted to the other. This is due to the fact that the ease of rotation about the single bond between the two phenyl nuclei leads to the facile interconversion of one salt to the other when in solu-

tion, thus resulting in an equilibrium mixture. Upon isolation of the salts, however, the less soluble precipitates first, and, as more is taken from the solution, the more soluble rearranges to the less soluble. Only by the use of different solvents can both salts of such a compound sometimes be isolated in solid form. The active salts thus obtained naturally show mutarotation in solution owing to the formation of an equilibrium mixture of the diastereoisomeric salts.

Non-Resolvable 2,2',6,6'-Tetrasubstituted Compounds. The following 2,2',6,6'-tetrasubstituted biphenyls^{68, 69, 70} (XXXII, XXXIII, XXXIV, XXXV), resolution of which could not be effected, were prepared. It appears, then, that these are truly 2,2',6,6'-tetrasubstituted biphenyls in which the *ortho* groups do not interfere sufficiently to allow resolution.



Resolvable but Easily Racemized Biphenyls. The compounds^{8, 16, 21} XXXVI and XXXVII were synthesized and found to racemize very easily when warmed in a neutral solvent. They are thus in sharp contrast to the stable active biphenyls earlier studied. Greater stability was found in XXXVIII.



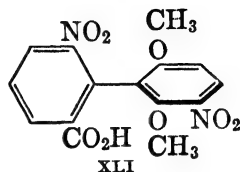
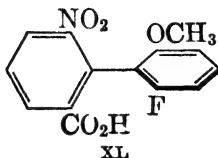
To make certain that the size was of primary importance and that no specific effect of the fluorine or methoxyl groups was involved, still

⁶⁸ Kleiderer and Adams, *J. Am. Chem. Soc.*, **55**, 4219 (1933).

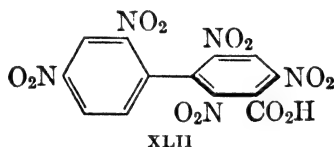
⁶⁹ Van Arendonk, Cupery, and Adams, *ibid.*, **55**, 4225 (1933).

⁷⁰ Becker and Adams, *ibid.*, **54**, 2973 (1932).

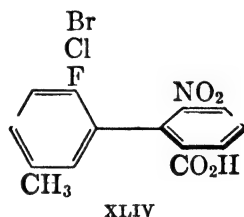
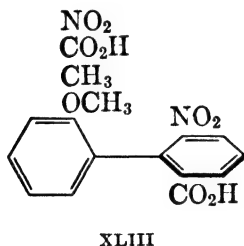
larger groups along with the fluorine and methoxyl groups were introduced into the molecule. The active forms of XXXIX do not racemize.²² In a similar manner XL and XLI give relatively stable active forms which racemize only slowly at higher temperatures.²⁸



Although the 2,2',6-trisubstituted biphenyls studied in the earlier researches could be racemized at high temperatures,³⁷ the active forms of XLII are perfectly stable under the usual conditions of racemization.



Relative Effect of Various Groups in Restricting Rotation. A direct comparison of the effect of different groups was obtained by a study of 2,2',6-trisubstituted biphenyls, in which the group in one position only was modified from member to member of the series. The two following sets of compounds were prepared:^{41, 44} (a) 2-X-2'-nitro-6'-carboxybiphenyl (XLIII), where X = methoxy, methyl, carboxyl, or nitro; and (b) 2-Y-5-methyl-2'-nitro-6'-carboxybiphenyl (XLIV), where Y = fluorine, chlorine, or bromine.

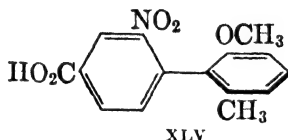


Evidence will be presented later to show that the presence of a 5'-methyl group in series XLIV probably has very little effect upon the racemization rates; therefore a direct comparison of the compounds XLIII and XLIV is permissible.

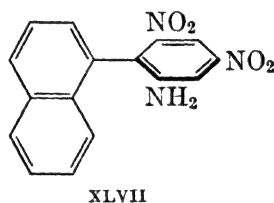
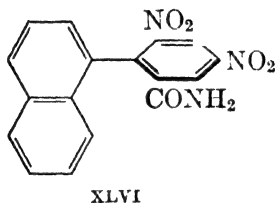
From the half-life periods it appears that the relative interference effects of the seven groups studied are in the following order: Br > CH₃ > Cl > NO₂ > CO₂H > OCH₃ > F. Racemization tests in various

solvents do not modify the results. It is interesting that the order from first to last parallels the decrease in the size of the groups as determined by x-ray data.

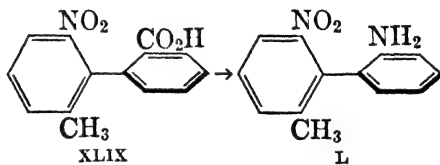
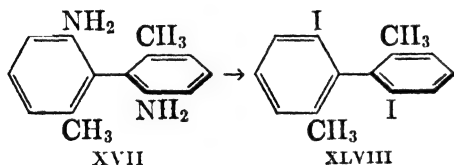
Experiments have been performed which demonstrate the methoxyl to have a greater hindering effect than the hydroxyl. It was found possible to resolve 2-methyl-4-carboxy-6-nitro-2'-methoxybiphenyl (XLV) but not the corresponding hydroxy compound.⁷¹



Replacement of a Group in the 2,2',6,6'-Position of an Optically Active Biphenyl. By a Hofmann rearrangement⁵² (p. 977), *d*-3,5-dinitro-6- α -naphthylbenzamide (XLVI) was converted into *d*-3,5-dinitro-6- α -naphthylaniline (XLVII) and the latter was obtained with a maximum rotation.



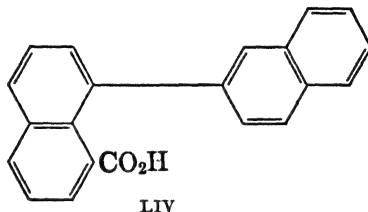
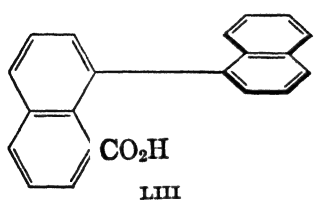
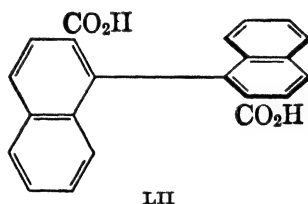
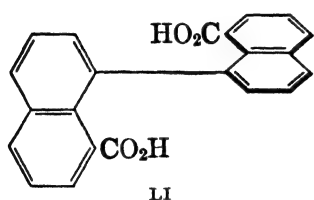
Active 6,6'-diamino-2,2'-bitolyl (XVII) was converted into active 6,6'-diiodo-2,2'-bitolyl (XLVIII), active 6-nitro-2-methyl-2'-carboxybiphenyl (XLIX) into active 6-nitro-2-methyl-2'-aminobiphenyl²⁷ (L),



and active 2-bromo-2'-amino-6,6'-bitolyl into active 2,2'-dibromo-6,6'-bitolyl.²⁵ The mechanism of such replacements is not clear. If the view is accepted that in these processes no free radicals are involved, no new deductions can be drawn from the experimental results. On the other hand, if free radicals are assumed as intermediates, it follows that the life period of the free radicals must be very short as compared with the time of rotation of the aromatic nuclei about the inter-nuclear bond.

⁷¹ Adams and Teeter, *ibid.*, **62**, 2188 (1940).

2,2'- and 2-Substituted Biphenyls. From the preceding discussion the possibility of resolution of certain 2,2'-disubstituted biphenyls would be predicted provided that the substituents are of proper size. Several investigators attacked this problem simultaneously. The resolution of LI was reported.^{72, 73, 74} This compound can be considered a disubstituted biphenyl with the C—CO₂H groups in the 2- and 2'-positions. The existence of optical isomers even though relatively unstable indicates that these groups are sufficiently large to interfere with the hydrogen atoms. The instability of this active compound as compared with that of its very stable isomer LII is striking. The preparation and resolution of LIII were also successful.⁷⁴ Its active forms are less stable than those of LI. A third compound (LIV) was found to be non-resolvable; hence



it appears that with only one substitution the molecule is much more mobile.

The optical resolution of several 2,2'-disubstituted biphenyls followed shortly: (LV),⁷⁵ (LVI),⁷⁶ (LVII),⁷⁷ (LVIII),⁷⁸ and the corresponding analog of LVIII with two methyl groups in place of the phenyls attached to the carbon holding the hydroxyl,⁷⁹ and (LIX)⁸⁰ and the corresponding bromide.⁸¹ The active forms of all these compounds are easily racemized substances.

⁷² Stanley, *ibid.*, **53**, 3104 (1931).

⁷³ Corbellini, *Atti. accad. Lincei*, **13**, 702 (1931).

⁷⁴ Meisenheimer and Beisswenger, *Ber.*, **65**, 32 (1932).

⁷⁵ Lesslie and Turner, *J. Chem. Soc.*, 2394 (1932).

⁷⁶ Lesslie and Turner, *ibid.*, 2021 (1932).

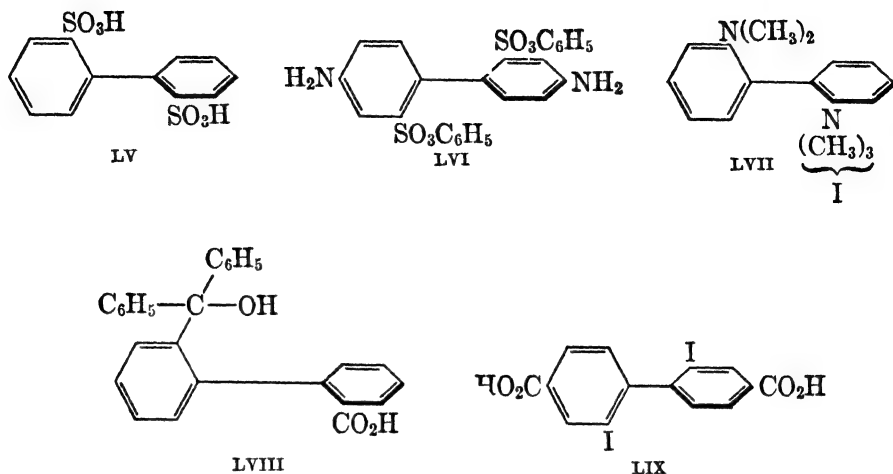
⁷⁷ Shaw and Turner, *ibid.*, 135 (1933).

⁷⁸ Corbellini and Pizzi, *Atti. accad. Lincei*, **15**, 287 (1932).

⁷⁹ Corbellini and Angeletti, *ibid.*, **15**, 968 (1932).

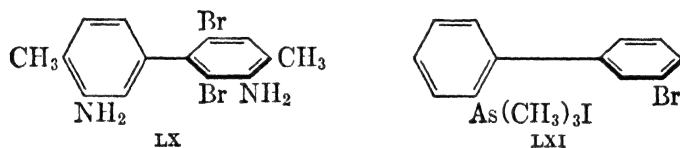
⁸⁰ Searle and Adams, *J. Am. Chem. Soc.*, **55**, 1649 (1933).

⁸¹ Searle and Adams, *ibid.*, **56**, 2112 (1934).

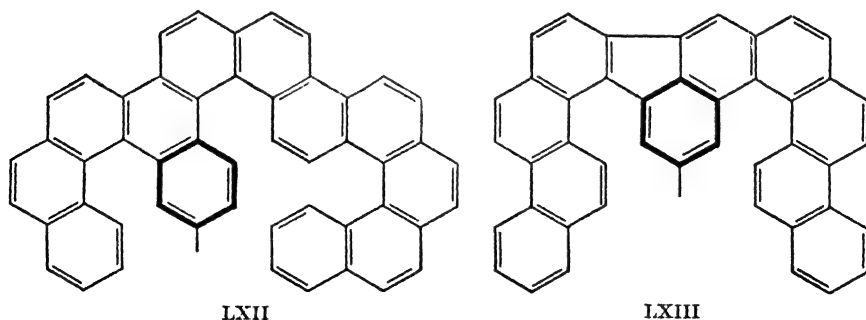


It is also interesting that the two *ortho* substituents may be in the same ring,⁸² as 2,6-dibromo-3,3'-diamino-4,4'-bitolyl (LX) was resolved. The active forms racemize slowly in solution.

The possibility of the resolution of a monosubstituted biphenyl is apparent, and partial success has been obtained.⁸³ The *d*-camphorsulfonate of 3'-bromobiphenyl-2-trimethylarsonium iodide (LXI) is reported to show some mutarotation.



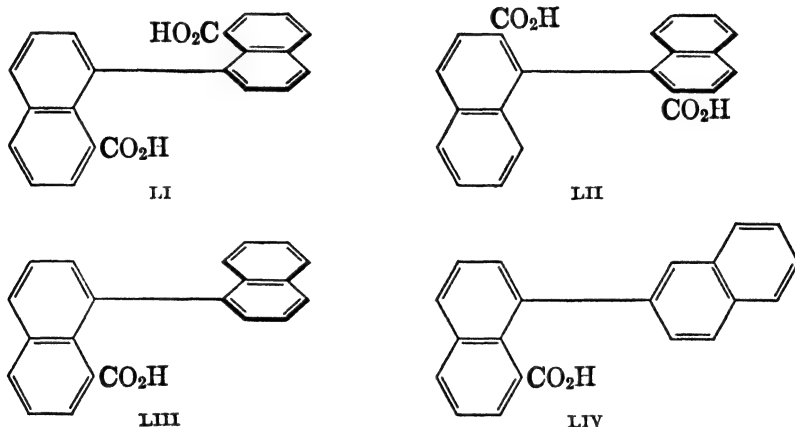
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⁸³ Leslie and Turner, *J. Chem. Soc.*, 1588 (1933); see also Adams and Cairns, *J. Am. Chem. Soc.*, **61**, 2179 (1939).

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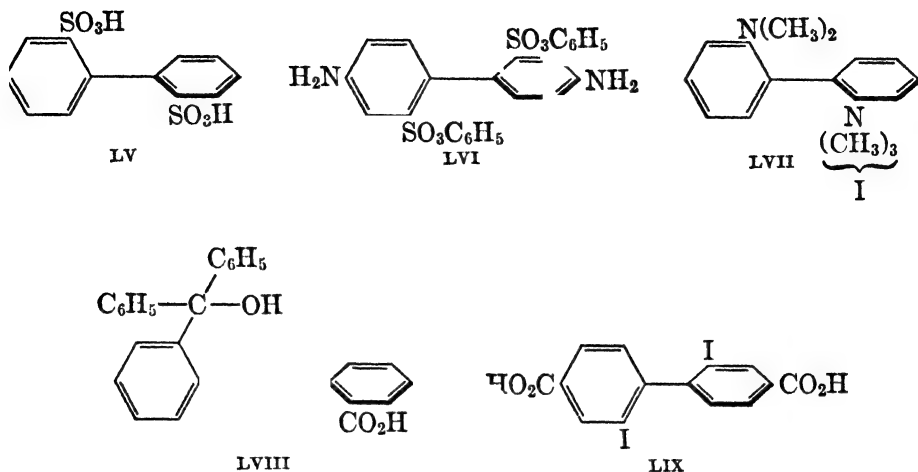
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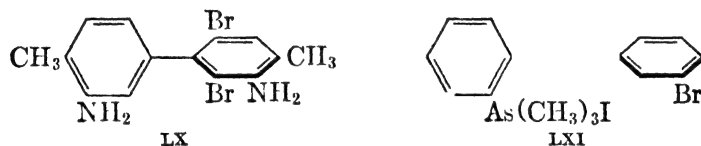
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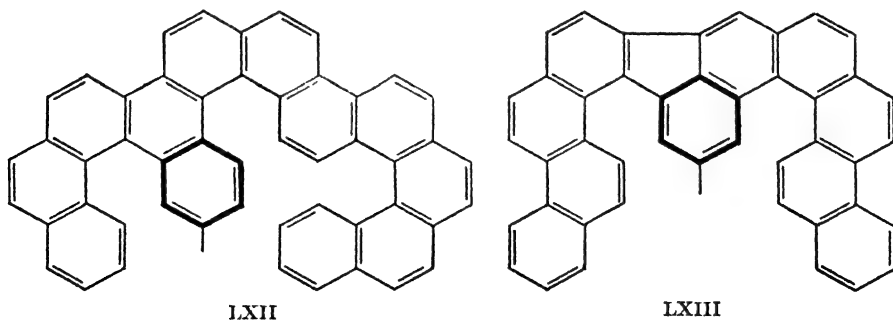


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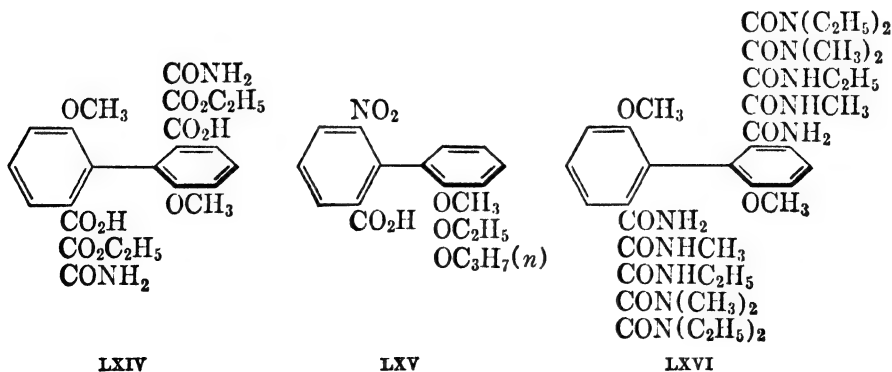
rotation exists at the pivot bond. Similarly, if two of the radicals shown in LXIII are substituted in the *para* positions of benzene, a molecule might be produced with two pivot bonds and two points of restricted rotation.

Steric Effects of Atoms or Groups Combined to the Atom Attached to the Ring. The steric effect of the hydrogens in the hydroxyl, the amino, or the methyl groups might be expected to be appreciable. Moreover, such an effect probably would be greater in the methyl than in the amino, and greater in the amino than in the hydroxyl group. Such influences undoubtedly would vary widely, though they probably would be small on account of the free rotation between the atom holding the hydrogens and the carbon atom of the ring to which it is attached. With larger nuclei combined to the atom attached to the ring, greater influences might be exerted, depending upon the sphere of influence and character of the atoms present.

An indication of what may be expected can be seen in a comparison of the racemization rates of the active acid, ester, and amide of 2,2'-dimethoxy-6,6'-dicarboxybiphenyl¹⁶ (LXIV). In glacial acetic acid the half-life periods of the acid, ester, and amide are 78, 88, and 240 minutes, respectively. The NH_2 part of the $-\text{CONH}_2$ group is sterically much more effective than an hydroxyl or ethoxyl in the same position.

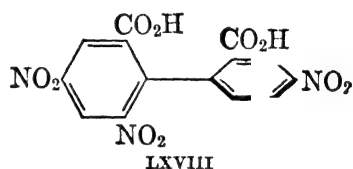
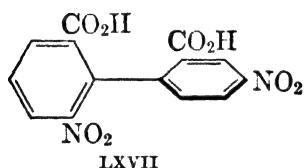
In a similar manner, a comparison was made of the racemization rate of 2-nitro-6-carboxy-2'-methoxybiphenyl⁴⁵ with those of the corresponding ethoxy and propoxy compounds (LXV). The ratio of half-life periods for the methoxy, ethoxy, and propoxy derivatives is approximately 1: 6: 8 in several of the common solvents.

Quite as interesting is a comparison of the racemization rates of various substituted amides of 2,2'-dimethoxy-6,6'-dicarboxybiphenyl⁸⁴ (LXVI). In these molecules the following order of stability is found: $-\text{NH}_2$ and $-\text{N}(\text{CH}_3)_2 < -\text{N}(\text{C}_2\text{H}_5)_2 < -\text{NHCH}_3 < -\text{NHC}_2\text{H}_5$.



⁸⁴ Hsing and Adams, *J. Am. Chem. Soc.*, **58**, 587 (1936).

Substituents in Positions Other than the 2,2',6,6'. Since the size of atoms or groups is due to the fundamental structure of the atoms involved, i.e., the nucleus and electron shells, it may be said that the electrical characteristics of atoms or groups are intimately associated with the size. On the other hand, the atoms or groups may be considered from the standpoint of polarity. Experiment shows that polarity or non-polarity plays an unimportant role. A comparison of biphenyl molecules containing four methyls, four chlorines, four nitros, four methoxyls, and four fluorines in the *ortho* positions has been made. The compounds were resolved and their racemization rates determined. The compounds containing the four chlorines and four nitro groups which are polar in character are very resistant to racemization. However, the compound with four methyl groups, which are essentially non-polar and of approximately the same size as the chlorines, is also very resistant to racemization. On the other hand, the tetrafluoro and tetramethoxy compounds are not even resolvable. In fact, from the behavior of the numerous compounds already studied, it is clear that size is the most important factor and that no correlation between the polarity and interference effects of the individual groups is possible. Steric influences due to the polarity of groups probably produce no more than a secondary effect which may be illustrated by properties of active molecules with additional groups substituted in positions other than the 2,2',6,6'. It was first noted⁶⁴ that the half-life period of the active compound LXVII in 2 *N* sodium hydroxide solution at 98° was 18 minutes, whereas that of LXVIII under the same conditions was 50



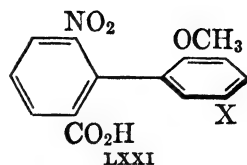
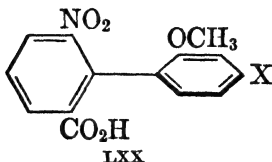
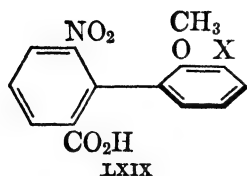
minutes. Thus, antipodally the latter was three times as stable as the former. This is inexplicable if the 2,2',6,6'-groups are the only factors which affect the stability to racemization of the active molecules.

Inspection of formulas LXVII and LXVIII shows that the only difference is a nitro group in the *para* position of one ring.

Later, Adams and his students studied a series of compounds with methoxyl, methyl, chlorine, bromine, and nitro substituted in the 3'-(LXIX),^{44, 85} 4'-(LXX),⁴³ and 5'-(LXXI)⁴² positions of 2-nitro-6-carboxy-2'-methoxybiphenyl, where X = OCH₃, CH₃, Cl, Br, NO₂.

⁸⁵ Yuan and Adams, *ibid.*, **54**, 2966 (1932).

These were compared with each other and with unsubstituted 2-nitro-6-carboxy-2'-methoxybiphenyl which racemizes readily at room



temperature and thus makes possible a fairly accurate polariscopic study of the rate of racemization. For each of the fifteen compounds, only one alkaloidal salt can be isolated and all these mutarotate in solution. The active acids obtained from the salts racemize readily in organic solvents at room temperature. Semi-quantitative data are given in Table I.

TABLE I
HALF-LIFE PERIODS IN MINUTES OF SUBSTITUTED
2-NITRO-6-CARBOXY-2'-METHOXYBIPHENYL

| Position of Substituent | Nitro | Bromo | Chloro | Methyl | Methoxy |
|-------------------------|-------|-------|--------|--------|---------|
| 3' | 1905 | 827 | 711 | 331 | 98 |
| 4' | 115 | 25 | 12 | 2.6 | 3.6 |
| 5' | 35 | 32 | 31 | 11.5 | 10.8 |

The 3' and 5' compounds were dissolved in ethyl alcohol for racemization studies; the 4' in acetone. The temperature used was 25° in all instances.

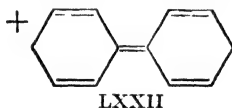
From these data it may be deduced that, within experimental error: (1) the stability to racemization of each series, whether the groups are substituted in the 3'- or 4'- or 5'-positions, is in the order: $H < OCH_3 < CH_3 < Cl < Br < NO_2$; (2) the stability to racemization of the 4'-substituted compounds is somewhat less than that of the 5'-substituted biphenyls and much less than that of the 3'-derivatives. One exception appears in that the 4'-nitro compound is more stable than the corresponding 5'-nitro derivative.

The theoretical basis for and the exact mechanism of this phenomenon are still obscure. One or more, or possibly all, of the following factors may be involved:⁴⁴ (1) the variation of the valency angle at which the *ortho* substituent on the ring is attached, thus changing the effective size of the group; (2) the modification of the internuclear distance between the carbon atom of the ring and the *ortho* substituent; (3) the slowing down of the semicircular oscillation of the two phenyl rings by substituents, thus diminishing the chances of the complete rotation; (4) the modification of the distance between 1,1' carbon atoms; (5) the bending of the linkage between the two rings in such a way that the rings are no longer coaxial.

The experimental results are perhaps significant in leading to the conclusion that cause (3) is not a factor, since the substitution of two atoms of similar polarity but of different weight, such as chlorine and bromine, results in almost identical effects on the rate of racemization. The order of increase in stability in the 3'-, 4'-, and 5'-series is the same as that of the dipole moments of the individual groups introduced into the positions indicated. The greater the dipole moment of the group the greater is the stability. There is no chemical evidence, however, to prove or disprove mechanisms 1, 2, 4, or 5.

It might appear at first, from the relatively large change in the racemization rates caused by substituents in positions other than the 2,2',6,6', that such substituents play a very important role. Nevertheless, it must be considered that the amount of change is something about which no quantitative information is available. It is quite possible that small changes in interference have a large observable effect, particularly on those molecules which are sensitive to racemization under mild conditions.

Calvin⁸⁶ has suggested that the non-resolvability of 2,2'-dibromo-4,4'-diaminobiphenyl in contrast to the resolvability of 2,2'-dibromo-4,4'-dicarboxybiphenyl may be explained on the basis of the amino groups inducing a greater tendency for formation of the ground state of the molecule (LXXII) which would prevent resolution.



Comparison of Isomeric 2,2',6-Trisubstituted Compounds. A series of biphenyls in which nitro, methyl, and carboxyl groups are interchanged in the 2,2',6-positions was studied. The racemization rates of the three compounds did not correspond to those which would be anticipated from the size of the groups as deduced from the study of the various 2,2',6,6'-tetrasubstituted biphenyls.⁴⁰ Similar anomalous results were observed in analogous molecules containing methoxyl, carboxyl, and nitro groups.⁸⁷

Comparative Rates of Racemization of Active Biphenyls and Their Salts. It is desirable to point out here another unexpected phenomenon which must be attributed to some factor in the molecule other than the size of *ortho* groups. The rates of mutarotation of the salts of the series of acids (LXIX), (LXX), and (LXXI) previously mentioned, in which a variable 3'-, 4'-, or 5'-group is involved, do not run parallel to the rates

⁸⁶ Calvin, *J. Org. Chem.*, **4**, 256 (1939).

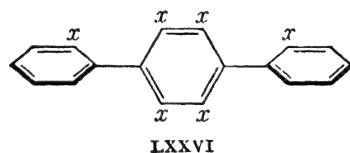
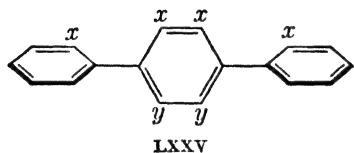
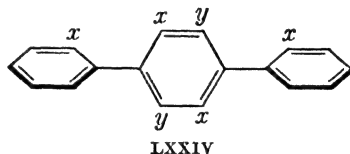
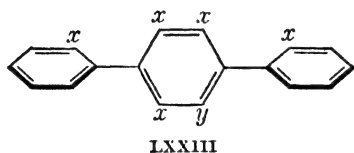
⁸⁷ Adams and Finger, *J. Am. Chem. Soc.*, **61**, 2182 (1939).

of racemization of the acids. The sodium salts of many optically active biphenyl derivatives racemize in aqueous solution more readily than the free acid racemizes in organic solvents. It was found, however, that the sodium salts of all the substituted 2-nitro-6-carboxy-2'-methoxybiphenyls in water racemize less readily than the free acids in organic solvents.⁴⁴ The sodium salts in absolute alcohol, on the other hand, racemize more readily than the free acids in the same solvent.

Polyphenyl Systems

Compounds having more than one asymmetric carbon atom possess a number of diastereoisomers, and the same phenomenon is to be expected in derivatives of properly substituted polyphenyls containing more than one pivot bond with restricted rotation.

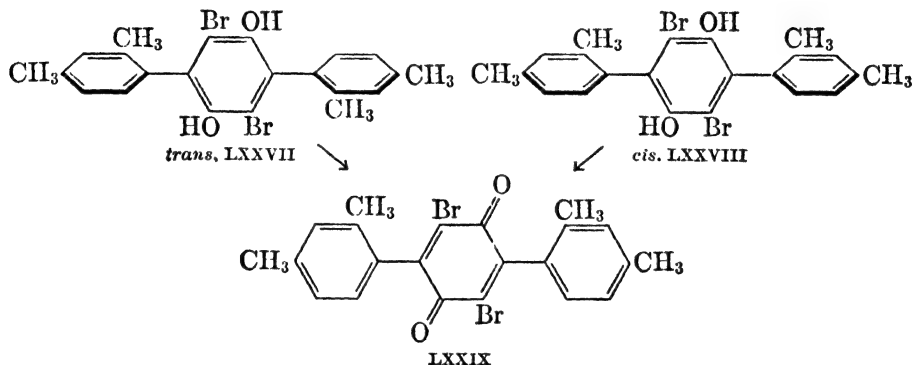
There are four general types¹ of properly substituted *p*-diphenylbenzenes, (LXXIII), (LXXIV), (LXXV), and (LXXVI). Type



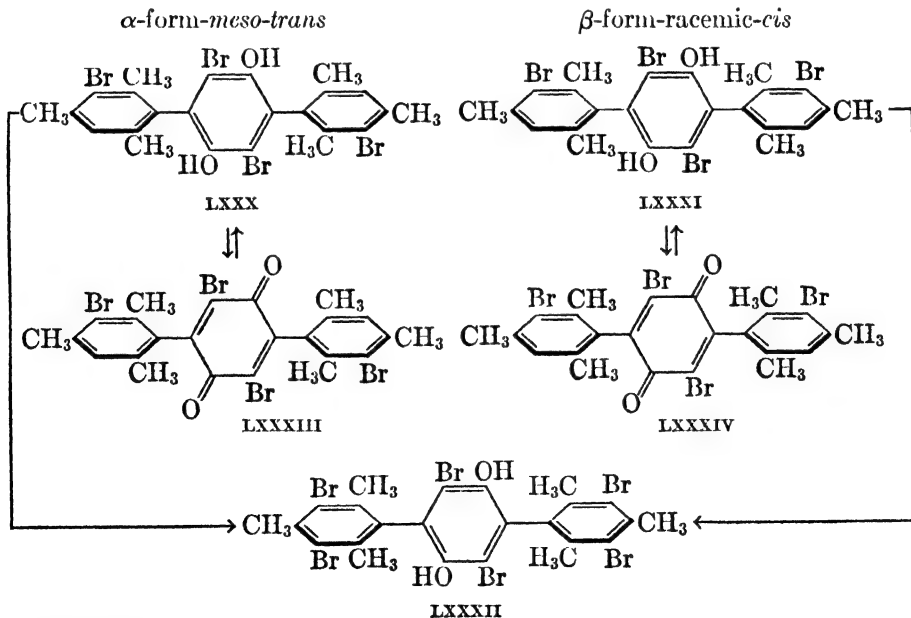
LXXIII should exist in two diastereoisomeric forms, each of which is a racemic modification, one *cis* and one *trans*. Compounds of types LXXIV and LXXV should exist in two forms, one *meso* and one racemic. The *meso* form of LXXIV is the *trans* form, and the racemic is the *cis* form. On the other hand, the *meso* form of LXXV is the *cis* form, and the racemic is the *trans* form. It is of interest that the *meso* form of LXXIV has not the usual plane of symmetry, but a point of symmetry. In type LXXVI the central ring is symmetrically substituted so no optical isomerism is possible. On the other hand, restricted rotation can still occur and two geometric isomers, *cis* and *trans* forms, result.

Properly substituted *m*- and *o*-diphenylbenzene derivatives yield analogous, though somewhat different, types of stereoisomers.¹ Quaterphenyls and more complex molecules of a similar type, when properly substituted, should exist in many modifications, the number of which can be calculated in the usual way.

Experimentally only *p*-diphenylbenzene derivatives have as yet been investigated. The possibility for the existence of a *meso* and a racemic modification of substituted *p*-diphenylbenzenes of type LXXIV was demonstrated by the isolation of two stereoisomeric compounds,⁸⁸ LXXVII and LXXVIII. Each of the two isomers forms individual series of derivatives but oxidizes to the same quinone (LXXIX). The quinone, in turn, upon reduction always gives a mixture of the two hydroquinones, (LXXVII) and (LXXVIII). Sufficient interference apparently is not present in the quinone to allow the existence of two isomers.



A second compound⁸⁹ (LXXX), in which all the *ortho* positions are filled, furnishes a more suitable compound for testing the validity of the predictions. The two stereoisomeric compounds (LXXX and LXXXI)



⁸⁸ Browning and Adams, *ibid.*, **52**, 4098 (1930).

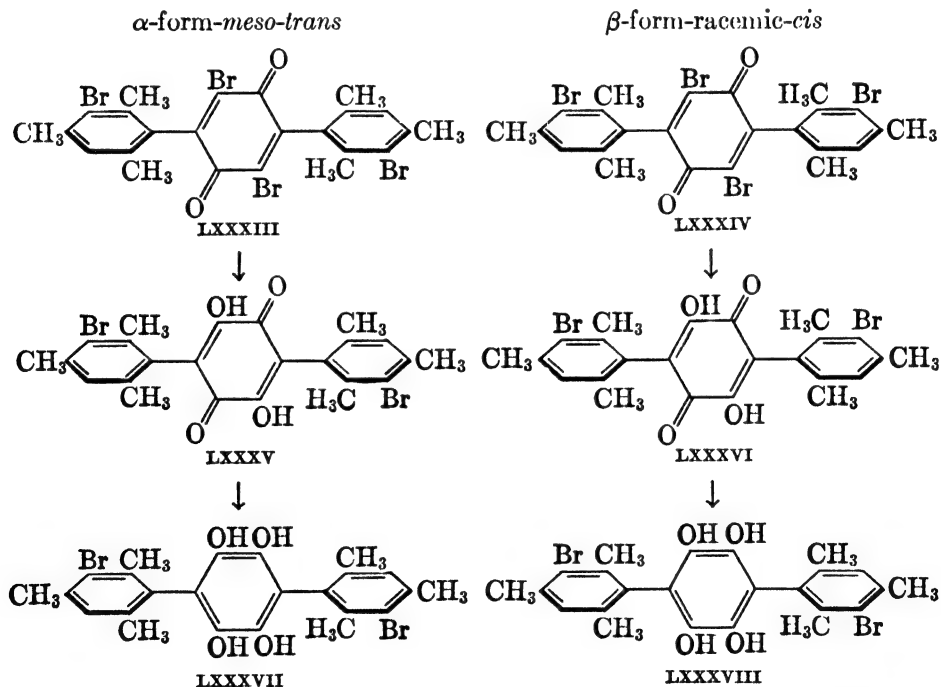
⁸⁹ Schildneck and Adams, *ibid.*, **53**, 343, 2203 (1931).

are converted readily to characteristic derivatives. Upon bromination they produce the same hexabromo derivative (LXXXII), thus experimentally confirming the fact that stereoisomers exist only if each of the rings is unsymmetrically substituted (p. 355).

Each of the two tetrabromodimesitylhydroquinones (LXXX and LXXXI), unlike the two dibromodixylylhydroquinones (LXXVII and LXXVIII), which oxidize to the same quinone, yields, upon oxidation, the corresponding stereoisomeric quinone (LXXXIII and LXXXIV).

The additional *o*-methyl group increases the interference sufficiently to produce restricted rotation and thus allows the formation of isomers in the quinones. Incidentally, these quinones present an example of restricted rotation between a benzene and a quinone ring.

The two diastereoisomeric dibromoquinones (LXXXIII and LXXXIV) with aqueous sodium hydroxide are converted to two stereoisomeric dihydroxyquinones (LXXXV and LXXXVI). These two latter compounds upon reduction yield the corresponding tetrahydroxy compounds (LXXXVII and LXXXVIII). The last three pairs belong to the *p*-diphenylbenzenes of type LXXVI and represent *cis* and *trans*



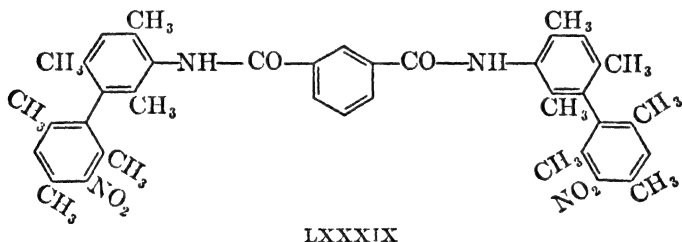
isomers incapable of optical isomerism. On the other hand, the two hydroxyquinones and their derivatives represent pairs of *cis* and *trans* isomers, in each pair of which one is a *meso* and one a racemic modification.

Owing to the small size of the hydroxyl group, the *cis* form of the dihydroxyquinone (LXXXVI) and its diacetate and dibutyrate can be converted, by heating in high-boiling solvents, into the corresponding *trans* forms. Similar treatment does not cause the conversion of any of the other *cis* forms in this series.

The high-melting forms in the dimesitylbenzene and dimesitylquinone series were assumed by analogy to other known pairs of stereoisomers to be the *trans* modifications, and the low-melting forms to be the *cis* modifications. That this assumption was correct was proved experimentally by the resolution of the *cis* form (LXXXI) and the non-resolution of the *trans* form (LXXX).⁹⁰

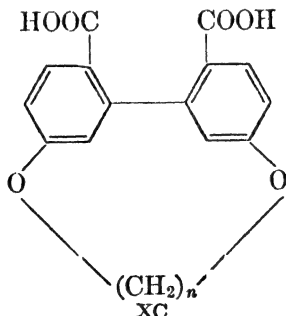
These results, though limited in number, show that in the diphenylbenzene system the exact conditions that would be expected from the study of the biphenyl series continue to hold.

A second type of molecule exhibiting two points of restricted rotation, with the points more widely separated than in the diphenylbenzenes just discussed, is represented by the isophthalamide of 3-nitro-3'-aminobimesityl (LXXXIX) which has been isolated in stereochemical forms, *meso* and racemic modifications.⁹¹



Restricted Rotation Due to a Many-Membered Ring in the 5,5'-Positions

A novel type of restricted rotation has recently been observed in 5,5'-(polymethylene)-diphenic acids (XC).⁶⁷ Diphenic acid cannot be



⁹⁰ Knauf, Shildneck, and Adams, *ibid.*, **56**, 2109 (1934).

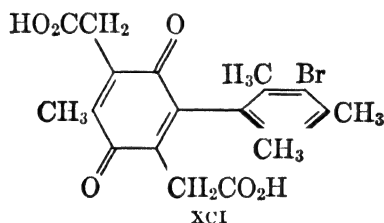
⁹¹ Adams and Joyce, *ibid.*, **60**, 1489 (1938).

resolved. The polymethylene bridge is capable of preventing the free rotation of the two nuclei, thus inducing in the molecule those properties resulting in asymmetry and hence in the possibility of optically active forms. The molecule containing eight methylenes in the chain has greater optical stability than that containing ten ($n = 8$, half-life 1955 minutes; $n = 10$, half-life 1491 minutes at 23° in dioxane). The racemization process in these molecules is assumed to be largely concerned with slippage of the carboxyl groups past one another. On this basis, the most obvious explanation for the difference in rates of racemization is that, the shorter the bridge across the 5,5'-positions, the less vigorous are the semicircular oscillations which the benzene nuclei undergo about the bond joining them.

Extension into Non-Benzenoid Ring Compounds

The search for the presence of stereoisomerism in certain substituted molecules containing rings of an aromatic but non-benzenoid type is a natural development from the study of biphenyl compounds. Such a field includes compounds in the series of the phenylpyridines, bipyridyls, phenylpyrroles, bipyrryls, phenylpyrazoles, etc. The difficulty of synthesis, however, is a severe hindrance to the study of these types.

Phenylquinones, Phenylpyrroles, Bipyrryls, Bipyridyls. In the study of terphenyl derivatives⁹¹ two stereoisomeric diphenylquinones (LXXXIII and LXXXIV) were obtained, and these compounds represent the first examples of a biphenyl type of isomerism in compounds where one of the rings is not a benzene nucleus. A simple phenylquinone (XCI) was also resolved into optical enantiomorphs.⁹²



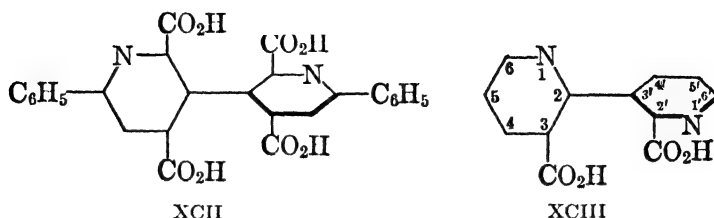
No phenylpyridines have as yet been resolved, but an optically active bipyridyl (XCII) which racemizes with ease was obtained.⁹³ Two salts with different rotations were obtained from 2,3'-bipyridyl-2',3-dicarboxylic acid (XCIII).⁹⁴

⁹² Hill and Adams, *ibid.*, **53**, 3453 (1931).

⁹³ Woodruff and Adams, *ibid.*, **54**, 1977 (1932).

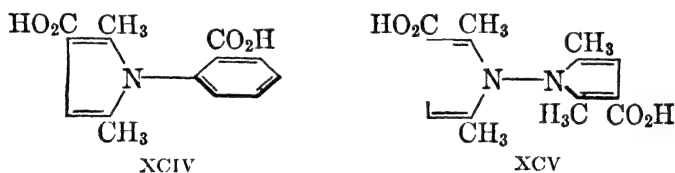
⁹⁴ Brydowna, *Roczniki Chem.*, **14**, 304 (1934); [*C. A.*, **29**, 2535 (1935)].

Perhaps the most fruitful and interesting results in the field of binuclear compounds other than biphenyls were obtained from the study of



compounds of N-phenylpyrrole and N,N'-bipyrrol types. These types differ from all the compounds previously studied in which both pivot atoms are carbon. Substituted N-phenylpyrroles represent a class of bicyclic compounds with carbon-nitrogen linkages between the rings, and substituted N,N'-bipyrrols, a class with nitrogen-nitrogen linkages between the rings.⁹⁵

The compound XCIV was resolved and the active forms were found to be exceedingly stable. Likewise, the optically active bipyrrols XCV proved to be unusually resistant to racemization.⁹⁶

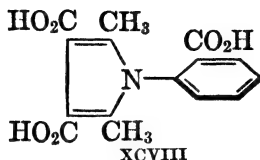
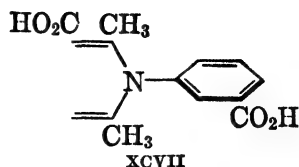
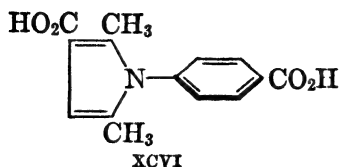


If the usual explanation of the phenomenon in the biphenyl series is applied here, there is restricted rotation between the benzene ring and the pyrrole ring or between the two pyrrole rings, owing to the interference of the *ortho* groups. In this case, the three valences of each nitrogen must be assumed to be in a single plane or at least to oscillate through a configuration in which the two rings are coaxial. With these assumptions, more or less the same conditions should hold for optical isomerism in phenylpyrroles as in the biphenyl series: groups of proper size substituted in the *ortho* positions and unsymmetrical substitution in each of the rings. Experimental facts have confirmed this view. It was impossible⁹⁷ to resolve any of the following compounds: XCVI, XCVII, and XCVIII. These represent examples of compounds with only two *ortho* substituents and an example of symmetry in one ring.

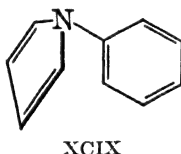
⁹⁵ Bock and Adams, *J. Am. Chem. Soc.*, **53**, 374 (1931).

⁹⁶ Chang and Adams, *ibid.*, **53**, 2353 (1931).

⁹⁷ Bock and Adams, *ibid.*, **53**, 3519 (1931).

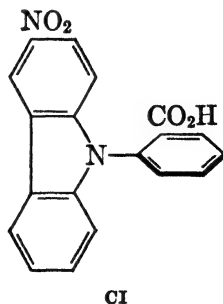
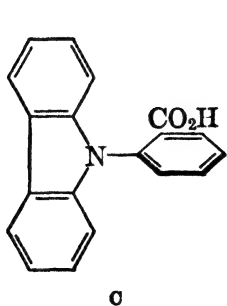


If a fixed tetrahedral structure for nitrogen and at the same time restricted rotation are assumed, formula XCIX might represent the appearance of such a molecule. Under these conditions unsymmetrical substitution in one ring only would be necessary to produce optical isomerism, but this does not agree with the facts (XCVIII).



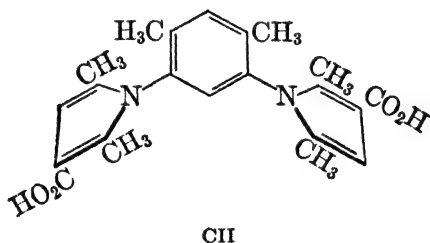
That optical isomerism in phenylpyrroles or bipyrryls might be due to an asymmetric nitrogen atom is also very improbable, first because of the lack of positive results of many investigators in resolving trivalent nitrogen compounds, and second because it is difficult to see how changes so slight as that from formula XCIV to formulas XCVII and XCVIII would eliminate optical isomerism if it were due to the nitrogen.

Analogous to N-phenylpyrroles are the N-phenylcarbazoles. It was found impossible⁹⁸ to resolve C, which contains the symmetrical carbazole ring, but optical isomers were readily obtained from CI which contains the unsymmetrically substituted carbazole.

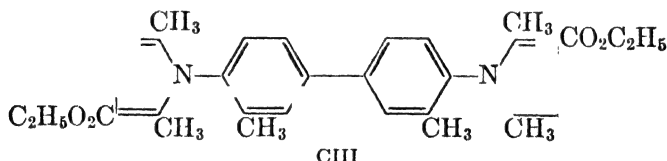


⁹⁸ Patterson and Adams, *ibid.*, **55**, 1069 (1933).

Dipyrrylbenzenes. As the experimental results indicate that phenylpyrrole isomerism is very similar to that in the biphenyl series, an extension is possible to dipyrrylbenzenes which should exhibit isomerism similar to that of the diphenylbenzenes. This was confirmed experimentally, and it was possible to distinguish the *meso* and the racemic modifications by resolution studies.⁹⁹ The diastereoisomeric forms of the *m*-dipyrrylbenzenes (CII) were obtained. The less soluble, presumably the *trans*, form is racemic and was resolved into its highly active, stable enantiomorphs, while the more soluble, presumably *cis*, form is



meso and could not be resolved. The compound CIII, 4,4'-bis-[1-(2,5-



dimethyl-3-carbethoxy)-pyrryl]-biphenyl represents a second molecule of this type and was isolated in two stereochemical forms. Similar results were obtained with the corresponding 2,5-dimethoxy derivative.¹⁰⁰

Other Types of Compounds with Restricted Rotation

The concept of restricted rotation has been applied experimentally to the stereochemistry of molecules other than biphenyls or bicyclic compounds.

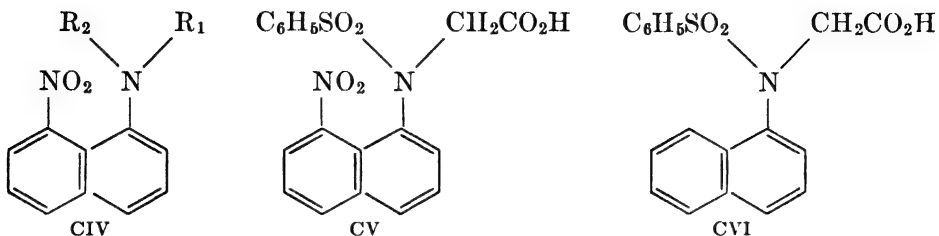
Carbon-Nitrogen Restriction. The prediction¹⁰¹ was made that steric hindrance similar to that which prevents free rotation of the two nuclei in biphenyl might be exhibited by *peri*-substituted naphthalenes (CIV). The nitro derivative (CV) was resolved into rather easily racemized enantiomorphous forms, whereas the unnitrated compound (CVI)

⁹⁹ Chang and Adams, *ibid.*, **56**, 2089 (1934).

¹⁰⁰ Adams and Joyce, *ibid.*, **60**, 1491 (1938).

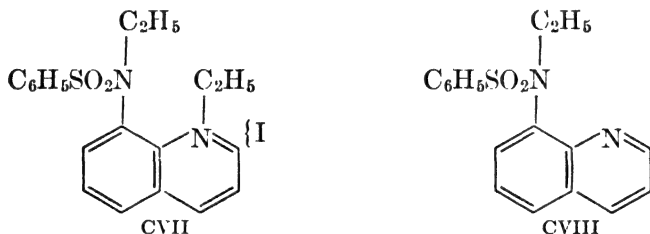
¹⁰¹ Mills and Elliott, *J. Chem. Soc.*, 1291 (1928).

could not be. This may be explained as molecular asymmetry due to restricted rotation about the C-N bond because of the collision of the R_1R_2N -group and the nitro group in the 8-position. No such obstacle

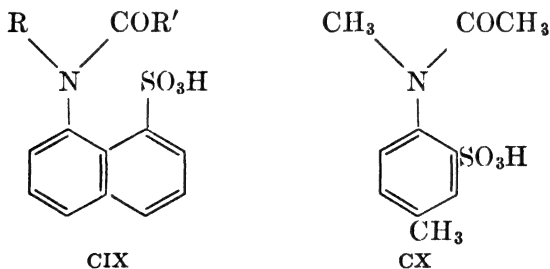


exists in the unnitrated compound (CVI), and hence there is no optical activity.

A second analogous illustration of restriction^{102, 103} is the resolution of CVII in contrast to the non-resolvability of the corresponding tertiary base (CVIII) or the corresponding 1-methylquinolinium iodide.



Mills and Kelham¹⁰⁴ prepared a series of 1-alkyl-acylamino-8-naphthalenesulfonic acids and resolved these compounds (CIX). The acetylmethylamino derivative possessed so high a degree of optical stability that the analogously constituted compound (CX) of the benzene series was also studied. The brucine salts of compound CX showed mutarotation when dissolved in chloroform. An active sodium salt was



¹⁰² Mills, *Trans. Faraday Soc.*, **26**, 431 (1930).

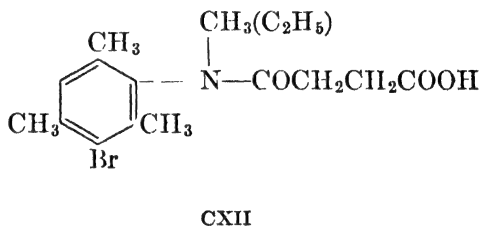
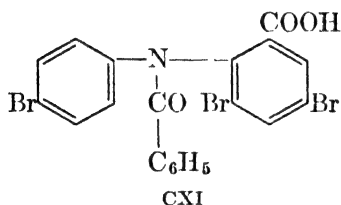
¹⁰³ Mills and Breckenridge, *J. Chem. Soc.*, 2209 (1932).

¹⁰⁴ Mills and Kelham, *ibid.*, 274 (1937).

also prepared which showed an initial $[\alpha]_{5461}$ of $+6.06^\circ$. It gradually racemized and gave a half-life period at 16.6° of 5.25 hours.

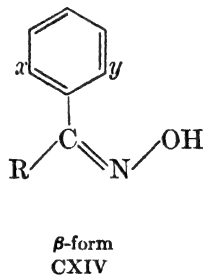
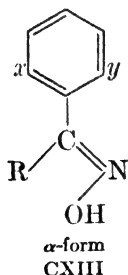
Other molecules in which restricted rotation between a nitrogen atom and a ring carbon atom exists have been described. Thus N-benzoyl-4,6,4'-tribromodiphenylamine-2-carboxylic acid (CXI) and several other compounds of a very similar type were shown to possess very weak optical stability presumably due to restricted rotation.¹⁰⁵

More striking in properties are the compound N-succinyl-N-methylbromomesidine (CXII) and the corresponding N-ethyl derivative



for their optically active forms possess remarkable stability in contrast to all the other previously described compounds (half-life of N-methyl 9 hours; of N-ethyl 28 hours in boiling *n*-butanol).¹⁰⁶ Owing to the fact that no molecules containing an asymmetric nitrogen atom have ever been obtained, the asymmetry in all these substances has been assumed to be due to restricted rotation. Confirmation of the soundness of this conclusion has been obtained experimentally by (1) bromination of an optically active form of compound CXII to an optically inactive dibromo derivative (the second bromine is substituted in the vacant position in the benzene ring) and (2) nitration of the same form to an optically active nitrobromo derivative.

Carbon-Carbon Restriction. Formulas CXIII and CXIV represent two forms of a substituted aromatic oxime.¹⁰⁷ In the molecule of the β -



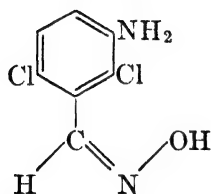
¹⁰⁵ Jamison and Turner, *ibid.*, 1954 (1937); 1646 (1938); 264 (1940).

¹⁰⁶ Adams and Dankert, *J. Am. Chem. Soc.*, **62**, 2191 (1940); Adams and Stewart, *ibid.*, **33**, 2859 (1941).

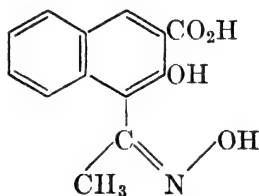
¹⁰⁷ Meisenheimer, Theilacker, and Beisswenger, *Ann.*, **495**, 249 (1932).

form of the ketoxime (CXIV), both the hydroxyl and the R groups have the possibility of colliding with the x and y groups on the benzene ring. Thus, the rotation of the radical $R-C=NOH$ would be restricted and the compound could exist in antipodal forms. In the α -form (CXIII) there would probably be no interference between the hydroxyl group and the x and y groups, so that the molecule should not be resolvable.

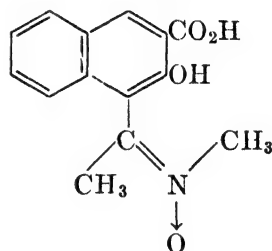
Experimentally, neither form of CXV could be resolved. Of the α - and β -forms of CXVI, the α -form could not be separated into enantiomorphs. The β -oxime of the same ketone (CXVI), however, yielded coniine, cinchonine, and strychnine salts, all of which exhibited mutarotation in pyridine; hence asymmetry of the molecules is inferred even though the optically active acid could not be isolated. The corresponding ether (CXVII) formed a cinchonine salt which mutarotated in solu-



CXV



(β -form)
CXVI



CXVII

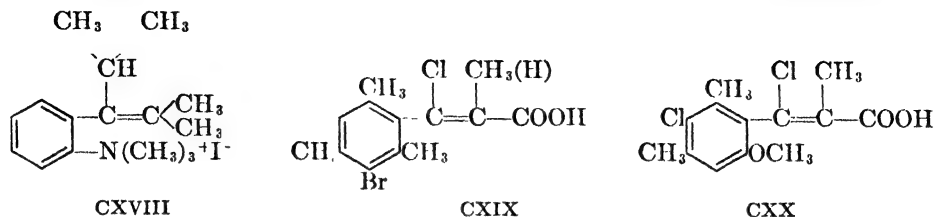
tion and upon decomposition at 0° gave an active ether. The resolution of these compounds may be used as evidence for the correctness of the Hantzsch-Werner theory for the structure of oximes, and offers a new instance of optical isomerism due to restricted rotation.

The most recent work in the field of molecules with carbon-carbon restricted rotation has consisted of a study of certain substituted aryl olefins. Many such compounds have now been prepared and resolved. The same principles obtain as in the substituted biphenyls. Thus Mills and Dazeley¹⁰⁸ observed that *o*-(β,β -dimethyl- α -isopropylvinyl)-phenyltrimethyl ammonium iodide (CXVIII) was readily obtained in optically active forms, and these forms proved to be very resistant to racemization. Adams and co-workers¹⁰⁹ have also succeeded in resolving a variety of aryl olefins illustrated by the structures CXIX and CXX. The α -methyl derivative of CXIX showed no racemization in boiling

¹⁰⁸ Mills and Dazeley, *J. Chem. Soc.*, 460 (1939); see also Maxwell and Adams, *J. Am. Chem. Soc.*, **52**, 2960 (1930).

¹⁰⁹ Adams and Miller, *J. Am. Chem. Soc.*, **62**, 53 (1940); Adams, Anderson, and Miller, *ibid.*, **63**, 1589 (1941); Adams and Binder, *ibid.*, **63**, 2773 (1941); Adams and Gross unpublished results.

butanol while the corresponding unsubstituted derivative had a half-life in boiling butanol of 200 minutes. On the other hand, the compound represented by CXX racemized in solvents at room temperature.

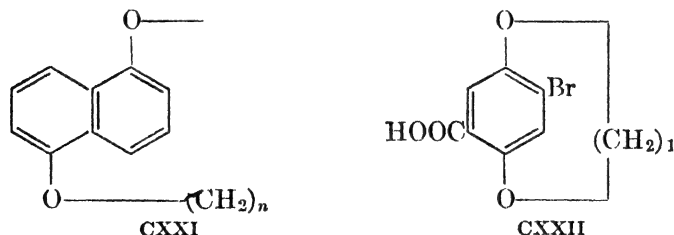


This case of racemization is undoubtedly due to the decrease in the interference arising from the difference in the size of the ring methyl and methoxyl groups. The β -(2-methyl-1-naphthyl)-acrylic acids showed remarkable optical stability but were less stable than the corresponding benzene derivatives.

The necessity of unsymmetrical substitution in such molecules was proved experimentally in the α -methyl derivative (CXIX) by (1) bromination of an optically active form to give an inactive dibromo derivative (the second bromine enters the vacant ring position) and (2) chlorosulfonation of the same molecule to an optically active bromochlorosulfonyl derivative.

As yet no successful experiments have been reported on the resolution of substituted diphenylmethanes, diphenylsulfones, or diphenylketones.^{59, 108, 110}

Carbon-Oxygen Restriction. Ziegler and Lüttringhaus¹¹¹ prepared by the high-dilution technique a variety of diethers illustrated by the general formula CXXI. They postulated that if the naphthalene nucleus were incapable of rotation within the many-membered ring, as would be



deduced from structural models, optical isomerism should be possible. Lüttringhaus and Gralheer¹¹² have demonstrated experimentally that

¹¹⁰ Maclean and Adams, *J. Am. Chem. Soc.*, **55**, 4683 (1933).

¹¹¹ Ziegler and Lüttringhaus, *Ann.*, **511**, 1 (1934).

¹¹² Lüttringhaus and Gralheer, *Naturwissenschaften*, **16**, 255 (1940).

such isomerism may result from the entwining of a many-membered ring around an otherwise symmetrical structure. They resolved the substituted benzoic acid (CXXII); its optical activity arises from the disposition of the decamethylenedioxy bridge either above or below the plane of the benzene nucleus. The active forms were very stable.

SUMMARY

In the foregoing section, a general discussion has been given of molecules which may be asymmetric owing to restricted rotation about a single bond. The two essential prerequisites for occurrence of optical isomerism in compounds of this type are: (1) restricted rotation of the planes of symmetry of the radicals about the pivot bond; (2) each of the radicals united by the pivot bond has one and only one plane of symmetry.

The only important class of such substances which has been studied experimentally is that of the substituted biphenyls and related compounds. The present status of this field can be summarized in the following four points:

(1) The stereoisomerism of substituted biphenyls and related compounds differs from all other types of stereoisomerism in that the number of forms cannot be defined by a type formula, but depends upon the specific properties of the univalent substituents.

(2) The resolution of certain substituted biphenyls and the non-resolution of others can be satisfactorily explained on the assumption that the two benzene rings in a resolvable biphenyl possess a common axis but lie in different planes, owing to the restriction of free rotation about the axis by the *ortho* substituents. The resulting configuration is asymmetric if the two rings are unsymmetrically substituted. The degree of restriction of rotation, as manifested by the ease of racemization, depends primarily upon the size of the *ortho* groups.

(3) The phenomenon persists in terphenyl compounds and binuclear compounds other than biphenyls.

(4) Restriction of free rotation about a single bond has been found also in properly substituted aryl olefins and aryl amines. An aromatic diether where a naphthalene nucleus is incapable of rotation within a many-membered ring has been prepared and resolved.

**PART IX. OPTICAL ACTIVITY OF FREE RADICALS, CARBANIONS,
AND CARBONIUM IONS**

Compounds containing only three groups attached to a central carbon atom fall into three classes, depending on the electronic distribution (pp. 585, 1928). The following formulas, Figs. 1, 2, and 3, indicate the three possibilities:

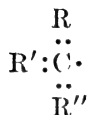


FIG. 1

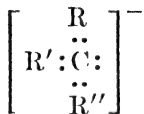


FIG. 2

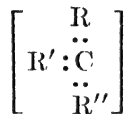


FIG. 3

The studies which have been made on the optical properties of these radicals have not yet reached a final satisfactory conclusion. The student should realize that the discussion in this chapter merely represents a summary of the evidence up to the present time. Much of the material is controversial, and the conclusions drawn are to a certain extent matters of opinion. The discussion should be read, therefore, with an open mind in order to get a general survey of the question of the optical activity of free radicals, carbanions, and carbonium ions.

Free Radicals (p. 581). A free radical (Fig. 4) is produced by the thermal dissociation of hexaphenylethane in non-ionizing solvents.

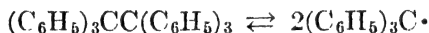


FIG. 4

If three different aryl groups are attached to the dissociating carbon atoms, then the free radical should be capable of existing in enantiomorphous forms (Figs. 5 and 6), provided that the single electron which occu-

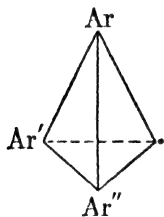


FIG. 5

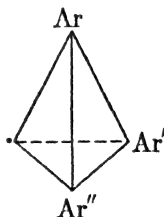


FIG. 6

pies one of the apices of the tetrahedron possesses the ability to keep the molecule optically stable. If it does not, then the molecules will racemize so rapidly that no optical activity can be observed.

Wallis and Adams¹ actually found that treatment of a solution of *l*-

¹ Wallis and Adams, *J. Am. Chem. Soc.*, **55**, 3838 (1933).

phenyl-*p*-biphenyl- α -naphthylthioglycolic acid with triphenylmethyl caused the optical activity of the solution to disappear. Evidently the free radical, phenyl-*p*-biphenyl- α -naphthylmethyl racemized as fast as it was formed.

Karagunis and Drikos² studied the action of chlorine on phenyl-biphenyl- α -naphthylmethyl in carbon tetrachloride solution under the influence of *d*- and *l*-circularly polarized light at two different wavelengths, $\lambda = 4350$ and $\lambda = 5890$. The reaction apparently involves the free radical, Fig. 7, and atomic chlorine, producing the triaryl chloride, Fig. 8,

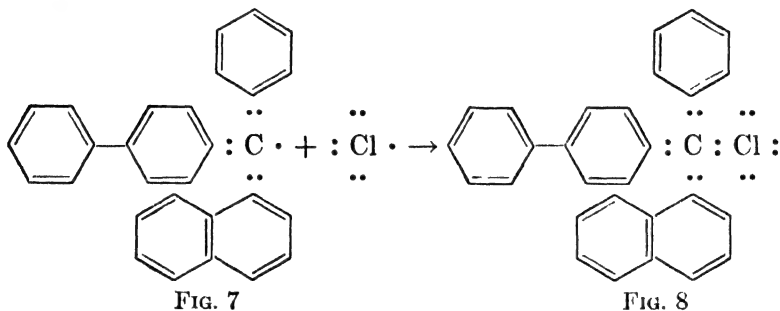


Fig. 8. The determination of the optical rotation of the solution at various intervals of time gave the curves shown in Fig. 9.

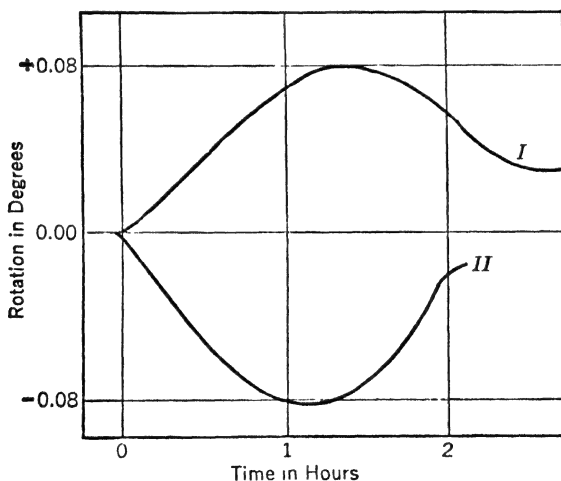


Fig. 9

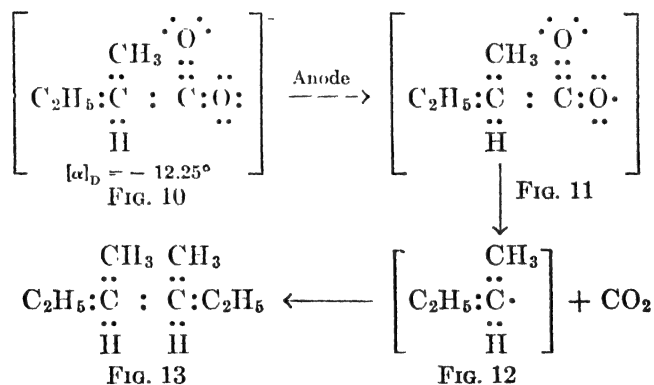
It will be noted that, at the end of an hour, the reaction products consisted of an excess of either *d*- or *l*-triaryl chloride, depending on the

² Karagunis and Drikos, *Naturwissenschaften*, **21**, 697 (1933); *Nature*, **132**, 354 (1933); *Z. physik. Chem.*, **26B**, 428 (1934).

kind of light used. After the reaction had proceeded to completion, equal amounts of *d*- and *l*-chloride were present—hence, optical inactivity. This asymmetric synthesis is of interest since it is the only study of such free radicals. It was found that neither *d*- nor *l*-circularly polarized light had any effect on either the triaryl chloride or on the free radical. The effect observed must hence be due to an acceleration of the reaction between the *d*- or *l*-form of the free radical and the activated chlorine atom. The work does not show that triarylmethyl radicals are optically active. The results may be interpreted, however, as indicating that the groups in a free radical are probably not planar. Up to the present time, no optically active free radicals definitely belonging to the type shown in Fig. 1 have been obtained.

Several different types of reactions have been investigated which may possibly involve a free radical of the type shown in Fig. 1 as an intermediate. In all reactions thus far investigated, the final products have been optically inactive.

The electrolysis of potassium *l*-ethylmethylacetate (Fig. 10) was found by Wallis and F. H. Adams³ to produce an optically inactive 3,4-dimethylhexane (Fig. 13). If the course of the reaction follows that indicated in the reactions below, the free radical, Fig. 12, is an intermediate. If this radical had been able to retain its asymmetry, then the combination of two *levorotatory* radicals should have produced the *levo* form of Fig. 13. The fact that the 3,4-dimethylhexane (Fig. 13)



was optically inactive indicates that the radical did not retain its asymmetry. It should be noted that the octane (Fig. 13) may exist in a *dl* and a *meso* form. The nature of the product was not determined.

If a Wurtz synthesis (p. 539) is carried out on an optically active alkyl halide, optically inactive hydrocarbons usually result. Thus,

³ Wallis and F. H. Adams, *J. Am. Chem. Soc.*, **55**, 3838 (1933).

Wallis and Adams³ obtained the same optically inactive 3,4-dimethylhexane mentioned above (Fig. 13) by the action of sodium on *d*-2-bromobutane (Fig. 14).

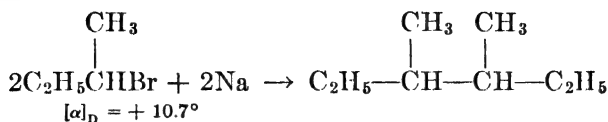


FIG. 14

FIG. 13

The action of sodium on *l*- α -bromobibenzyl (Fig. 15) also produced the optically inactive 1,2,3,4-tetraphenylbutane.³ (Fig. 16).

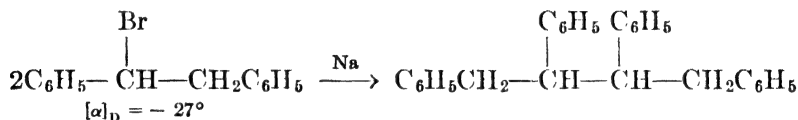


FIG. 15

FIG. 16

The optical inactivity of the products of the Wurtz reaction indicates that racemization occurred at some intermediate stage, since both the initial and final products were stable.

If the radical (Fig. 18) formed by the action of sodium on the alkyl halide racemizes rapidly then the hydrocarbon formed by the combina-

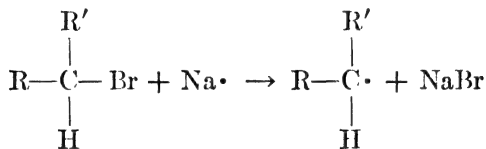


FIG. 17

FIG. 18

tion of two of these *dl*-radicals would be optically inactive and consist of a mixture of the *dl* and *meso* forms. On the other hand, if a sodium alkyl (Fig. 19) is produced rapidly, it may react with the optically active

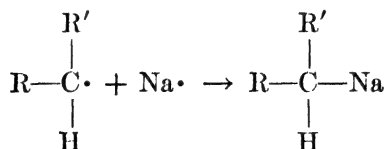
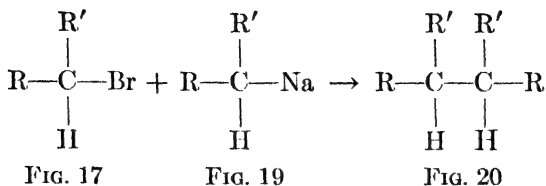
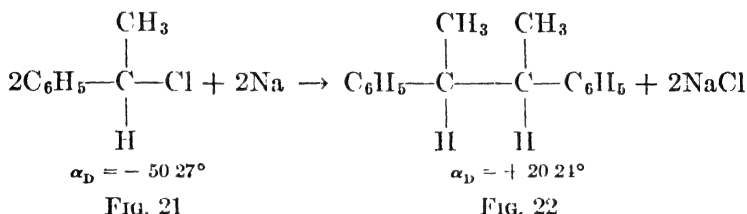


FIG. 19

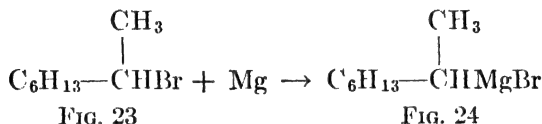
bromide (Fig. 17) to form a hydrocarbon which may contain some of the optically active form.



Actually Ott⁴ obtained optically active *d*-2,3-diphenylbutane (Fig. 22) by the action of sodium on *l*-methylphenylchloromethane (Fig. 21) along with some of the *meso* form of the hydrocarbon while the recovered chloride was racemized to some extent.



The formation of the Grignard reagent from an optically active halide also results in an optically inactive⁵ product (p. 516). Thus, the action of magnesium on *d*-2-bromoöctane (Fig. 23) results in the optically inactive 2-octylmagnesium bromide⁶ (Fig. 24). By analogy to the Wurtz reaction, it might be possible that similar radicals are involved.



Also, when *d*- or *l*-2-chloroöctane was treated with lithium and the resulting 2-octyllithium carbonated, the acid obtained was optically inactive.⁷

With the exception of the experiments of Ott cited above, it is evident that racemization occurs when an organometallic compound is formed from an optically active halide in which the halogen is attached to the asymmetric carbon atom.

The photochemical or peroxide catalyzed chlorination of *d*-1-chloro-2-methylbutane (Fig. 25) yielded optically inactive 1,2-dichloro-2-methylbutane⁸ (Fig. 26). If the mechanism is that represented by the chain

⁴ Ott, *Ber.*, **61**, 2124 (1928).

⁵ Pickard and Kenyon, *J. Chem. Soc.*, **99**, 65 (1911); Schwartz and Johnson, *J. Am. Chem. Soc.*, **53**, 1063 (1931).

⁶ Porter, *J. Am. Chem. Soc.*, **57**, 1436 (1935).

⁷ Tarbell and Weiss, *ibid.*, **61**, 1203 (1939).

⁸ Brown, Kharasch, and Chao, *ibid.*, **62**, 3435 (1940); Kharasch, Kane, and Brown *ibid.*, **63**, 526 (1941).

reactions (a), (b), and (c), it is evident that the intermediate alkyl radical underwent racemization.

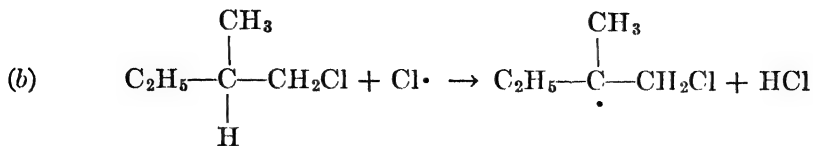


FIG. 25

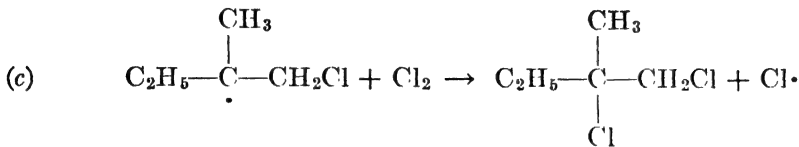


FIG. 26

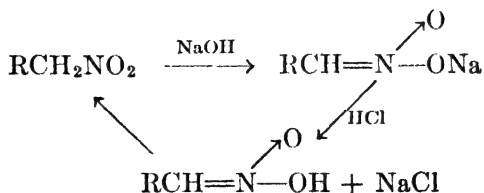
Carbanions. If a pair of electrons occupies the fourth valence of the central carbon atom resulting in the negative ion shown by Fig. 2, then such *carbanions* might exist in enantiomorphic forms if they are stable to racemization.

Numerous studies of the salts of aliphatic secondary nitro compounds have been made to determine whether these compounds constitute examples of optically active anions. The fact that primary and secondary nitro compounds exist in two tautomeric forms was established by the work of Hantzsch and Schultze.⁹ The two forms of phenylnitromethane and their properties are shown in Table I.

TABLE I

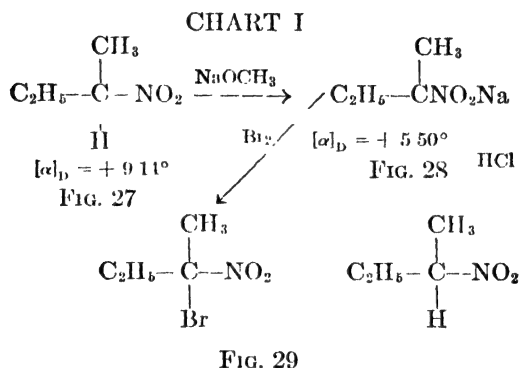
| | |
|---|--|
| $\text{C}_6\text{H}_5\text{CH}_2\text{NO}_2$ | $\text{C}_6\text{H}_5\text{CH}=\text{N}-\text{OH}$ |
| Liquid | Solid |
| Stable normal form | M. P. 84° |
| Insoluble in Na_2CO_3 | Labile <i>aci</i> -form |
| No reaction with $\text{C}_6\text{H}_5\text{NCO}$ | Soluble in Na_2CO_3 |
| No color with FeCl_3 | Reacts with $\text{C}_6\text{H}_5\text{NCO}$ |
| Non-electrolyte | Red color with FeCl_3 |
| | Electrolyte |

The solid *aci*-form is obtained by the addition of acid to a cold solution of the sodium salt, and readily tautomerizes to the normal nitro modification.

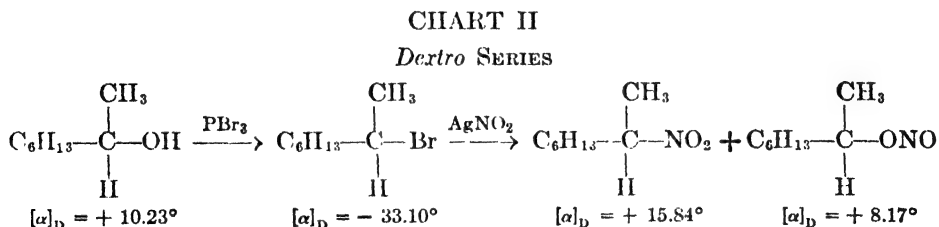


⁹ Hantzsch and Schultze, *Ber.*, **28**, 699, 2251 (1895).

The change from the *aci*-form to the normal form may be followed by conductivity measurements.¹⁰ This summarizes the general status of these nitro compounds and their salts up to 1927, when Kuhn and Albrecht¹¹ made the startling observation that *d*- or *l*-2-nitrobutane (Fig. 27) upon treatment with methanolic sodium methoxide gave optically active solutions of the sodium salts (Fig. 28) (See Chart I). Acidification of the salt regenerated a partially active nitrobutane, and bromination formed optically active 2-bromo-2-nitrobutane (Fig. 29).



Since the Victor Meyer reaction between an alkyl halide and silver nitrite is known to produce an alkyl nitrite as well as a nitro-alkane, a series of experiments was carried out with *d*-, and *l*-2-bromoöctane. The optically active 2-octyl nitrite was separated from the active 2-nitroöctane¹² (Chart II). It was again observed that *d*-, and *l*-2-nitroöctane gave optically active salts which regenerated an optically



active compound upon acidification. Bromination was also reported to produce an optically active bromonitro compound.

¹⁰ Branch and Jaxon-Deelman, *J. Am. Chem. Soc.*, **49**, 1765 (1927).

¹¹ Kuhn and Albrecht, *Ber.*, **60**, 1297 (1927).

¹² Shriner and Young, *J. Am. Chem. Soc.*, **52**, 3332 (1930).

The resolution ¹³ of phenyleyanonitromethane (Fig. 30) by means of brucine and conversion of this brucine salt into an optically active sodium salt (Fig. 31) was also reported in 1932.

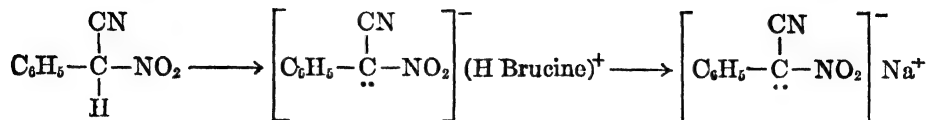


FIG. 30

FIG. 31

All these observations led to a reconsideration of the older formulas, Figs. 32, 33, 34, for the nitro compounds and their salts.

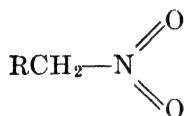


FIG. 32

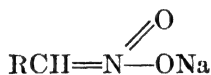


FIG. 33

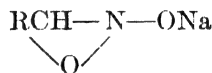


FIG. 34

On the basis of the fundamental postulates of the electron theory (p. 1821), the formulas, Fig. 32 and Fig. 33, are impossible, since they would place ten electrons in the valence shell of nitrogen. The classical formula, Fig. 33, proposed by Nef ¹⁴ for the salts obviously cannot account for their optical activity. The structure, Fig. 34, originally proposed by Holleman ¹⁵ and by Hantzsch and Schultze,⁹ has always been regarded as a possibility, but never generally accepted, chiefly because the existence of such carbazoxy rings has never been absolutely established. Figure 34 also does not satisfactorily explain the ready conversion of the salts into the bromonitro compounds.

Since 2-methyl-2-nitropropane does not form a salt with sodium ethoxide it is evident that the sodium alkoxide does not add to the nitro group. The electronic formula for the nitro compound is shown by Fig. 35 and the formulas for the salts by Figs. 36, and 37. The anion, Fig. 36, is optically inactive and would produce the *dl*-nitro compound on acidification. In Fig. 37, the α -carbon atom is asymmetric and treatment with acid would regenerate the original active nitro compound.

The chief objection to such an assumption is the fact that racemization of the compound (Fig. 37) does not occur readily. Shriner and

¹³ Mills, *J. Soc. Chem. Ind.*, **51**, 750 (1932).

¹⁴ Nef, *Ann.*, **280**, 263 (1894).

¹⁵ Holleman, *Rec. trav. chim.*, **13**, 405 (1894).

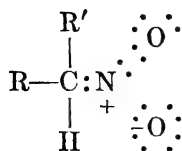


FIG. 35

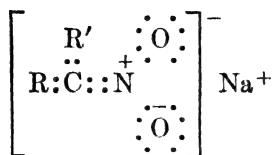


FIG. 36

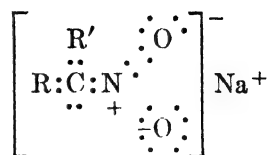


FIG. 37

Young¹² suggested that it must be stabilized by combination with the solvent, the anion forming a hydrogen bond with the ethanol (Fig. 38). Evidence supporting this concept has been obtained by Ray and Palinchak,¹⁶ who resolved 9-nitro-2-benzoylfluorene with brucine. The brucine salt contained alcohol of crystallization, and hence this salt would be

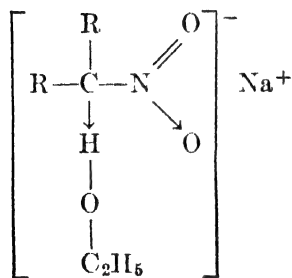


FIG. 38

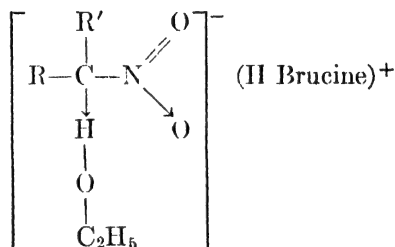


FIG. 39

represented by Fig. 39. Neither the free *aci*-9-nitro-2-benzoylfluorene nor its potassium salt was active.

This concept of an optically active carbanion, stabilized by solvation, seemed reasonable enough at the time (1927–1930) because other optically active compounds such as the sulfoxides, sulfinic esters, sulfilmines, and sulfonium salts were known whose electronic structures placed an unshared pair of electrons at one apex of a tetrahedron. However, the development of the theory of resonance (page 1943) and its application to aliphatic nitro compounds leads to the view that the acidity of nitro-alkanes is a consequence of resonance stabilization of the

¹⁶ Ray and Palinchak, *J. Am. Chem. Soc.*, **62**, 2109 (1940).

anion produced by removal of the α -hydrogen. The resonance forms of the anion are shown by Figs. 40 and 41. In fact, it is postulated that

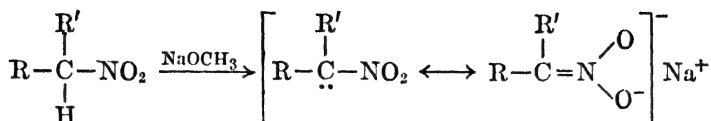


FIG. 40

FIG. 41

the contribution of structure 41 is more important than that of the structure of Fig. 40. From the resonance standpoint, therefore, the salts derived from optically active secondary nitro-alkanes should be optically inactive.

This anomalous situation has recently been cleared up by Kornblum, Lichtin, Patton and Iffland¹⁷ who have shown that the Victor Meyer reaction is more complicated than hitherto believed. For example, the above investigators found that silver nitrite reacted with *l*-2-bromo-octane to produce not only *d*-2-nitro-octane and *d*-2-octyl nitrite, but also *d*-2-octyl nitrate, *d*-2-octanol, 2-octanone and other by-products. Moreover, the *d*-2-nitro-octane and *d*-2-octyl nitrate distilled together and could not be separated by fractionation. Treatment of the mixture of the two with aqueous alkali dissolved the nitro-compound but not the nitrate which was separated in the optically active form. The solution of the salt of the *d*-2-nitro-octane was optically inactive. The pure *d*-2-nitro-octane, obtained by treatment with cold 96% sulfuric acid which dissolved the nitrate, gave optically inactive salts upon treatment with sodium ethoxide and the bromo-nitro-octane produced by bromination was also optically inactive. A similar series of experiments was carried out starting with *d*-2-bromo-octane and again the carefully purified *l*-2-nitro-octane gave optically inactive salts. It thus seems evident that the salts of secondary nitro compounds should be represented by the resonance structures of Figs. 40 and 41, and that they are not examples of optically active carbanions.

¹⁷ Kornblum, Lichtin, Patton and Iffland, *J. Am. Chem. Soc.*, **69**, February (1947).

A totally different type of molecule containing the optically active negative ion shown by Fig. 2 has been postulated by Wallis³ as an intermediate in the following reactions which were carried out in liquid ammonia.

The fact that the compound (Fig. 44) is optically active would require the intermediate ion (Fig. 43) to retain its asymmetric configuration, and hence would indicate that the unshared pair of electrons acts as the fourth group at one apex of the asymmetric carbon atom (*). The alkylsodium, Fig. 43, was not isolated. If its formation involves a mechanism similar to that discussed for the Wurtz reaction (p. 386), then it should be a racemic form. It is possible that complete conversion of Fig. 42 into the alkylsodium, Fig. 43, did not occur, and that the

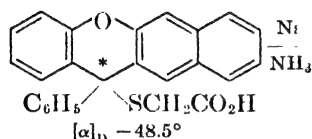


Fig. 42

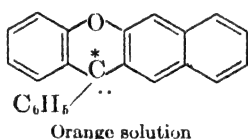


Fig. 43

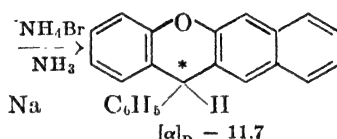


Fig. 44

final optically active compound was produced by reduction of the thioglycolic acid derivative upon addition of the ammonium bromide to the sodium in liquid ammonia. Even if this should be the case, the reaction still involves the replacement of the $-\text{SCH}_2\text{CO}_2\text{H}$ group on the asymmetric carbon atom by hydrogen, and means that the intermediates, whatever they may be, retain their tetrahedral configuration.

Certain sulfones constitute another class of compounds which react with alkalis to produce salts in which the negative ion is a carbanion. In order that salts may be readily formed, at least two sulfonyl groups should be attached to a carbon atom which carries a hydrogen atom. Thus, Shriner, Struck, and Jorison,¹⁸ from a study of the properties of methylenediphenyl disulfone, Fig. 45, concluded that salt formation leads to the carbanion, Fig. 46. These salts may be readily alkylated

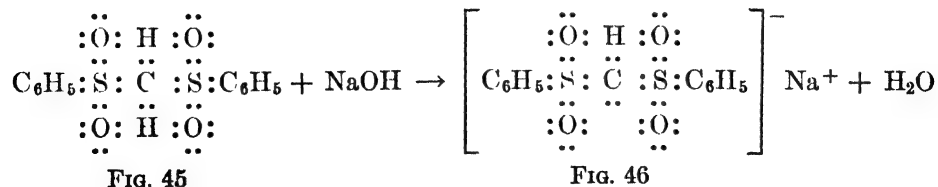


Fig. 45

Fig. 46

and brominated, but give no color with ferric chloride solution. The sulfone, Fig. 45, does not react rapidly with bromine in carbon tetra-

¹⁸ Shriner, Struck, and Jorison, *ibid.*, **52**, 2060 (1930).

chloride solution, and also gives no color with ferric chloride solution. It should be noted that in these molecules the oxygen atoms are attached to the sulfur atoms by semi-polar bonds, and hence no true enol forms may exist, since such a structure would place ten electrons in the valence shell of sulfur. These molecules constitute specific cases in which the residual negative charge of the carbanion undoubtedly resides on the central carbon atom. That this effect is due to the sulfonyl groups and not to the phenyl groups was shown by Shriner and Stutz¹⁹ from a study of methylene di-*n*-butyl disulfone. Arndt and Martius²⁰ reached similar conclusions regarding the non-enolization of disulfonylmethanes. If the structure, Fig. 46, for these salts is accepted, then a properly substituted unsymmetrical disulfone should yield salts of the structure shown in Fig. 47, which should be capable of existing in optically active forms.

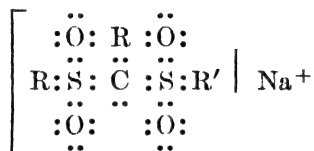


FIG. 47

The studies on the sulfones have involved the synthesis of properly substituted disulfones in an optically active state, and then conversion into salts in order to determine whether the salts, corresponding to Fig. 47, were optically active.

Kipping²¹ synthesized the disulfones shown in Figs. 48, 49, 50, and 51.

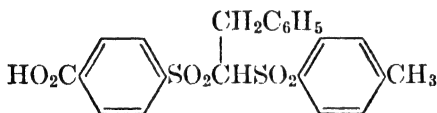


FIG. 48

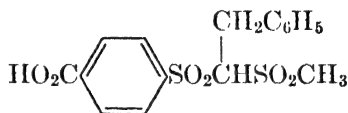


FIG. 49

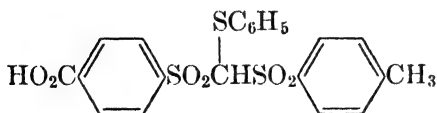


FIG. 50

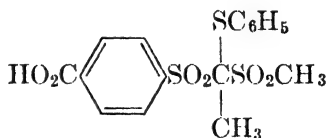


FIG. 51

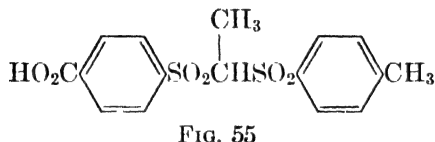
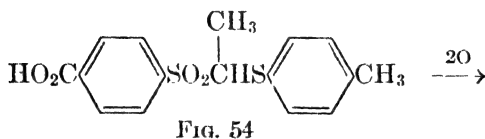
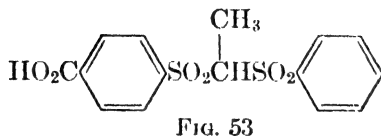
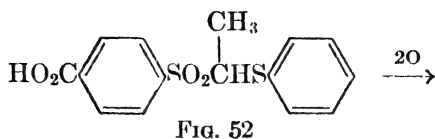
The first three of these compounds could not be resolved, but the fourth (Fig. 51) was resolved into *d*- and *l*-forms by means of brucine and *l*-menthylamine. This disubstituted sulfone, Fig. 51, is quite stable to acids and alkalis.

¹⁹ Shriner and Stutz, *ibid.*, **55**, 1242 (1933).

²⁰ Arndt and Martius, *Ann.*, **499**, 228 (1932).

²¹ Kipping, *J. Chem. Soc.*, 18 (1935).

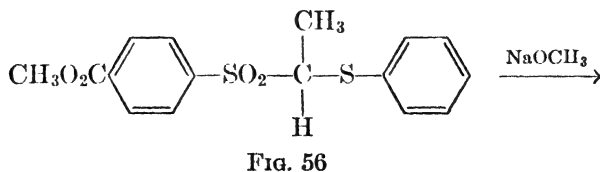
Kipping ²¹ was successful in resolving the thiosulfones, Figs. 52 and 54, into their optically active forms. Oxidation of the optically active forms, Figs. 52 and 54, produced the disulfones, Figs. 53 and 55, respec-



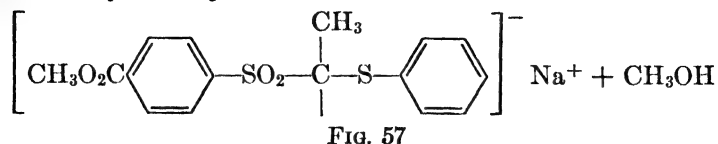
tively, but these disulfones were always the racemic modifications. No optically active disulfones containing at least one hydrogen on the central carbon atom could be obtained. If both hydrogens were replaced, as in Fig. 51, then resolution was successful, which indicates that, in the presence of the basic compounds used in the resolutions, the carbanions of the type shown in Fig. 47 are not stable.

A study of the properties of the compound, Fig. 52, showed that it did not racemize in acetic acid solution or in sodium hydroxide solution as long as only one equivalent of alkali was present. If more than one equivalent of alkali was added, then racemization occurred rapidly. Esterification of the compound, Fig. 52, produced the optically active methyl ester, Fig. 56.

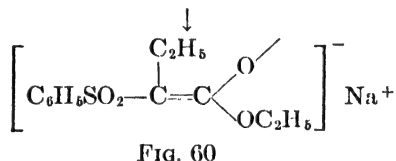
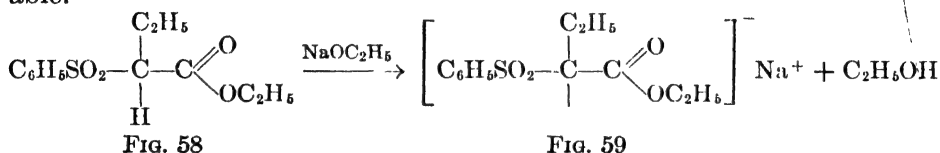
Treatment of this ester with small amounts of sodium methoxide



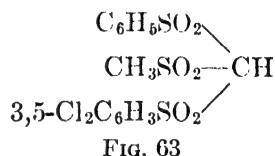
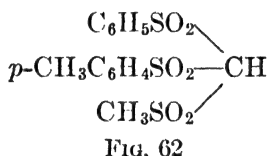
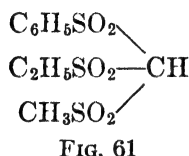
caused racemization, which indicated that the carbanion, Fig. 57, did not retain its asymmetry.



Ashley and Shriner²² prepared ethyl *l*- α -phenylsulfonbutyrate (Fig. 58), and found that treatment with sodium ethoxide caused immediate racemization, even though the reaction was carried out at -10° . Evidently the carbanion, Fig. 59, immediately racemized or tautomerized to the enolate ion, Fig. 60. The latter explanation appears more probable.



In 1931, Gibson²³ succeeded in synthesizing three unsymmetrical trisulfones with the structures shown in Figs. 61, 62, and 63.



All three of these sulfones were distinctly acidic and readily formed salts with alkalis. The brucine salt of the compound, Fig. 61, was readily prepared and crystallized, but decomposition with ammonia gave an inactive salt. Attempted resolutions with the active hydroxyhydrindamines also failed. The trisulfones, Fig. 62 and Fig. 63, failed to produce crystalline salts with alkaloids, and could not be resolved.

Certain rearrangements (p. 981) involving optically active radicals have been carried out. Jones and Wallis²⁴ studied the Curtius rearrangement, and Wallis and Nagel²⁵ the Hofmann rearrangement of

²² Ashley and Shriner, *J. Am. Chem. Soc.*, **54**, 4410 (1932).

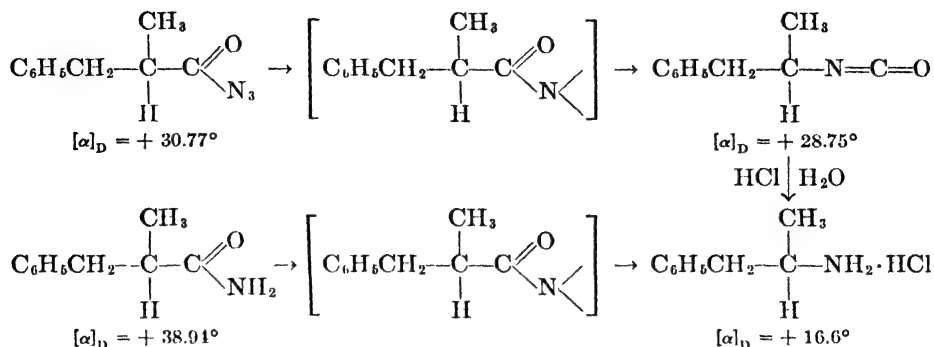
²³ Gibson, *J. Chem. Soc.*, 2637 (1931); *Chem. Rev.*, **14**, 431 (1934).

²⁴ Jones and Wallis, *J. Am. Chem. Soc.*, **48**, 169 (1926).

²⁵ Wallis and Nagel, *ibid.*, **53**, 2787 (1931).

optically active azides and amides. The reactions are summarized in Chart IV.

CHART IV



The point to be noted is that, in the rearrangement of the intermediate compound in the brackets, the asymmetric carbon atom must detach itself from the carbon of the carbonyl group and attach itself to the nitrogen atom. The fact that the final amine is optically active means that the intermediate retained its asymmetry. It appears that the optically active radical migrates with its pair of electrons without ever actually separating as a carbanion. Recently Lane and Wallis²⁶ have found that the Wolff rearrangement of optically active diazoketones also produces optically active products provided that no enolizable α -hydrogen atom is present.

Carbonium Ions. Many investigations have been carried out which have had for their primary purposes the elucidation of the question of the optical stability of carbonium ions and the mechanism of the reactions involved. A large number of such replacement reactions was studied in connection with the Walden inversion. Biilmann,²⁷ for example, represents the formation of the active lactic acids from the optically active α -bromopropionic acids by the following equations, and ascribes the failure of the intermediates to racemize to the charges on the dipolar ion (p. 1088) (Fig. 64). McKenzie and Clough²⁸ and later

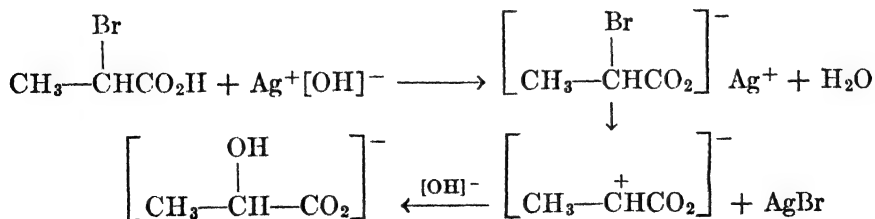


FIG. 64

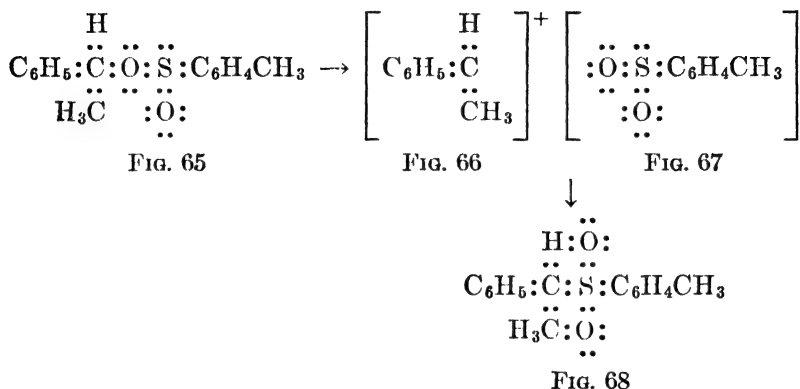
²⁶ Lane and Wallis, *J. Org. Chem.*, **6**, 443 (1941).

²⁷ Biilmann, *Ann.*, **388**, 330 (1912).

²⁸ McKenzie and Clough, *J. Chem. Soc.*, **103**, 687 (1913).

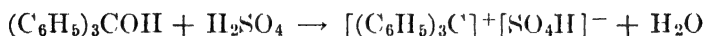
McKenzie, Roger, and Wills²⁹ after reviewing numerous reactions conclude that the free electric charge can stabilize the configuration of a tervalent carbonium ion.

Kenyon and Phillips³⁰ studied the rearrangement of the active sulfinic ester shown in Fig. 65. The product of the rearrangement was the optically inactive sulfone, Fig. 68.

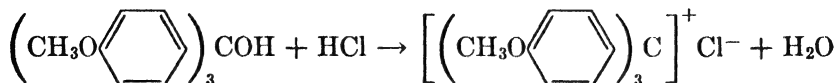


The rearrangement occurs spontaneously, and no reagents are involved, hence the process may involve a momentary separation into the positive carbonium ion, Fig. 66, and the negative sulfinate ion, Fig. 67. In the starting material both the carbon and sulfur atoms are centers of asymmetry, but dissociation causes the formation of the symmetrical sulfinate ion (Fig. 67) so the sulfur loses its asymmetry. Since the sulfone was inactive it follows that the carbonium ion also underwent racemization.

Some of the most interesting types of carbonium ions are the halochromic salts which are produced when triarylcaminols are dissolved in strong mineral acids. These salts, which may be isolated in the solid state, are formed by the elimination of a molecule of water from the carbinol and the acid. They are ionic compounds, the positive charge appearing on the carbon atom, and hence are called *carbonium salts*. For example, triphenylcarbinol yields a colored salt with sulfuric acid



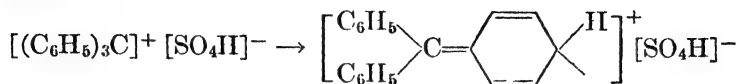
and the tri-*p*-methoxy derivative yields a salt even with aqueous hydrochloric acid.



²⁹ McKenzie, Roger, and Wills, *ibid.*, 779 (1926).

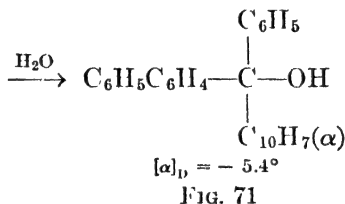
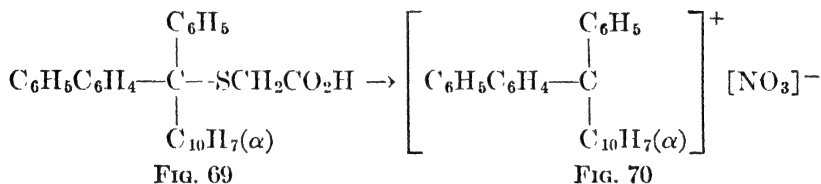
³⁰ Kenyon and Phillips, *ibid.*, 1676 (1930)

It should be noted that these salts are separate and distinct compounds in contrast to triphenylchloromethane, $(\text{C}_6\text{H}_5)_3\text{CCl}$, which is not colored and not a salt. It does form a colored carbonium complex with aluminum chloride with the formula $[(\text{C}_6\text{H}_5)_3\text{C}]^+ [\text{AlCl}_4]^-$. Since the salts are highly colored it is probable that tautomerization to a quinoid form occurs.

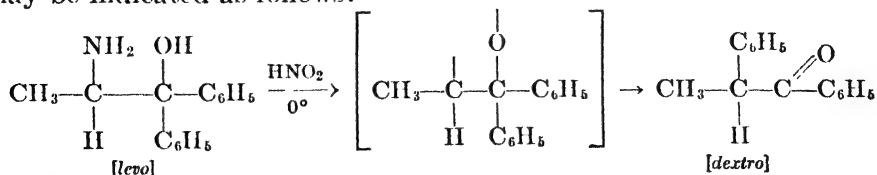


The preparation of optically active triarylmethane derivatives is very difficult, and only a few such compounds are known. Wallis³¹ prepared and resolved phenylbiphenyl- α -naphthylmethylthioglycolic acid (Fig. 69). Gomberg and Gordon³² showed that the halochromic salts of this active triarylmethane derivative are optically inactive.

Wallis and Adams³ made the interesting observation that silver nitrate in aqueous acetone solution converts the compound, Fig. 69, into an optically active carbinol. The intermediate may be the positive carbonium ion, Fig. 70, and must retain its asymmetric configuration in order to produce the active carbinol, Fig. 71.



McKenzie, Roger, and Wills³³ have carried out a semi-pinacolinic deamination of an optically active amino alcohol. The transformations may be indicated as follows:



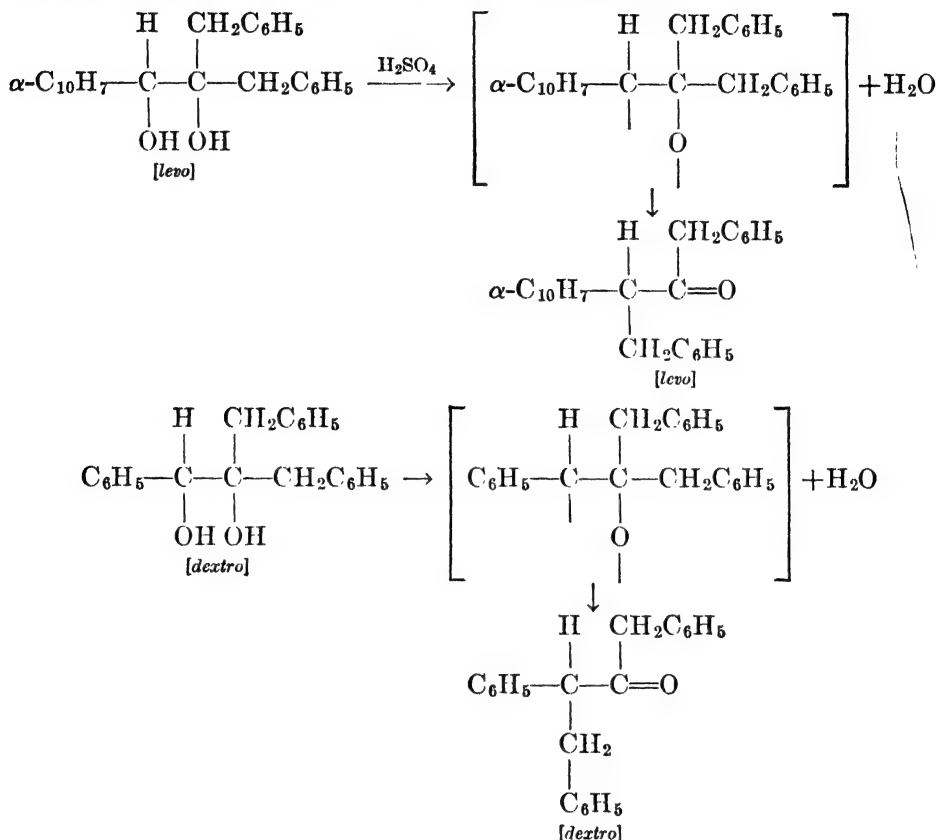
³¹ Wallis, *J. Am. Chem. Soc.*, **53**, 2253 (1931).

³² Gomberg and Gordon, *ibid.*, **57**, 119 (1935).

³³ McKenzie, Roger, and Wills, *J. Chem. Soc.*, 779 (1926); Roger and McKenzie, *Ber.* **62**, 272 (1929).

Here the intermediates retain their asymmetry even during the migration of the phenyl radical. The stabilization of the intermediate radicals is ascribed to the charges present.

The pinacol-pinacolone rearrangement has also been studied by McKenzie,³⁴ who succeeded in obtaining optically active ketones from active glycols, as indicated in the following reactions:



The intermediates apparently retain their asymmetry and may contain a carbonium carbon but the exact mechanism has not been established.

PART X. OPTICAL ISOMERISM OF ELEMENTS OTHER THAN CARBON

The *general principles* outlined in the previous discussion of carbon compounds apply equally well to compounds containing other elements. For optical isomerism to exist, the molecule must be asymmetric, and this asymmetry may be achieved by the general structure of the entire

³⁴ McKenzie, *J. Soc. Chem. Ind.*, **50**, 926 (1931).

molecule or by an individual asymmetric atom. As has been indicated in the introduction, optical isomers of compounds of many elements are known. The synthesis and resolution of these asymmetric molecules have almost always involved the presence in the molecule of substituted hydrocarbon groups or radicals, and hence they are of interest and importance to the organic chemist.

The elements which give rise to optical isomerism in their compounds may be classified into three groups according to whether the spatial distribution of their valence forces is tetrahedral, octahedral, or planar.

Elements with a Tetrahedral Distribution of Their Valencies

The tetrahedral group will be considered first, and the isomerism of compounds of each element discussed. In fact, it is the existence of optical isomers of the compounds of these elements which has led to the conclusion that their valencies are tetrahedrally distributed. Such elements are:

Si, N, S, Se, Te, Sn, Ge, P, As, B, Be, Cu, Zn, Pt, Pd

Silicon. This element is in the same group of the periodic table as carbon, and is tetravalent. It forms a series of hydrides or silanes, SiH_4 , Si_2H_6 , Si_3H_8 , and Si_4H_{10} , analogous to the paraffin hydrocarbons. Various alkyl silanes have been prepared, and if the four groups are different the silicon atom becomes asymmetric and optical isomers become possible. In 1910, Challenger and Kipping¹ prepared and resolved the tetrasubstituted silane shown in Fig. 1 by crystallization of the brucine

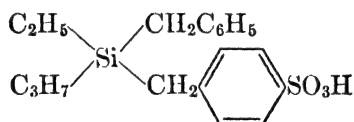


FIG. 1

salts. In earlier investigations² the more complicated silicon compound shown in Fig. 2 was prepared. It should exist in two inactive

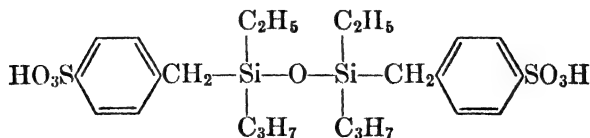


FIG. 2

¹ Challenger and Kipping, *J. Chem. Soc.*, **97**, 142, 755 (1910).

² Kipping, *ibid.*, **91**, 209 (1907); Luff and Kipping, *ibid.*, **93**, 2090 (1908).

forms corresponding to a *meso* and a racemic modification. Evidence indicating the resolution of a form corresponding to the latter into the *d*- and *l*-forms was obtained by means of the *d*-methylhydrindamine salts. From a stereochemical point of view, therefore, this compound is analogous to tartaric acid.

Nitrogen. The stereochemical nature of nitrogen in its compounds has been more thoroughly investigated than that of any other element with the exception of carbon. Numerous arguments and discussions concerning the distribution of the valencies in trivalent and so-called pentavalent nitrogen compounds have appeared in the literature, and many spatial models of the nitrogen atom have been proposed. In the light of present-day knowledge of molecular structure, much of this material is now incorrect. Hence, the discussion of the stereoisomerism of nitrogen compounds which follows is not entirely an historical résumé, but an attempt to set forth the modern viewpoint and to interpret the past experimental evidence.

Trivalent Nitrogen Compounds. The electronic formulas for ammonia and a tertiary amine are shown in Figs. 3 and 4. If the nitrogen atom is

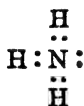


FIG. 3

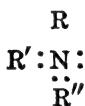
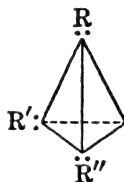


FIG. 4



d-form
FIG. 5

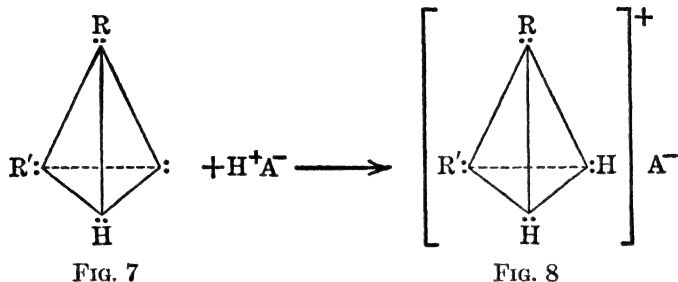


l-form
FIG. 6

tetrahedral, then a tertiary amine with three different groups should be capable of existing in the optically isomeric forms shown by Figs. 5 and 6 in which the nitrogen atom is represented by the tetrahedron. The three different radicals are placed at three of the apices, and the fourth apex contains the unshared pair of electrons.

The history of the attempts to resolve trisubstituted nitrogen compounds is a long, interesting chapter in organic chemistry. In fact, the early investigators were doomed to disappointment before they started. They attempted to resolve ethylbenzylamine, benzylhydroxylamine, methylaniline, tetrahydroquinoline, and tetrahydropyridine, which are secondary amines (Fig. 7) and form salts having symmetrical cations of the ammonium type (Fig. 8) and, therefore, are not resolvable. These early investigators regarded the nitrogen in ammonium salts as pentavalent, and all valencies equivalent. In these early attempts, *d*-tartaric acid was used exclusively as the resolving agent.

This error, however, was quickly rectified by later investigators who attempted to resolve the following tertiary amines: methylethyl- β -



naphthylamine, methyl-*n*-propylaniline, benzyl-*p*-nitrobenzylhydroxylamine and kairolin by means of *d*-camphor-10-sulfonic acid or *d*-3-bromocamphor-8-sulfonic acid. The results were totally negative.

Wedekind and Klatte³ studied the *d*-camphor-10-sulfonic acid and *d*-3-bromocamphor-8-sulfonic acid salts of 1-phenyl-2,3-dimethyl-4-(methylethylamino)-5-pyrazolone (Fig. 9), and 1-phenyl-2,3-dimethyl-4-(methylbenzylamino)-5-pyrazolone (Fig. 10).

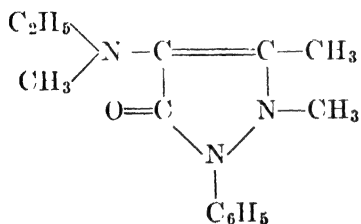


Fig. 9

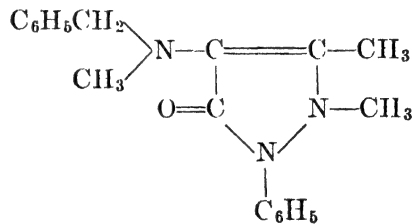


Fig. 10

Although fractional crystallization of these salts showed changes in the rotatory values of the fractions, decomposition of the salts gave only the inactive bases.

Up to this time practically all the attempts to resolve trisubstituted nitrogen compounds had been carried out by addition of the active acid to the "asymmetric" nitrogen atom to produce the salt. Other investigators, realizing that this was undesirable, used a group other than that of the "asymmetric" nitrogen atom as the resolving substituent. This modification gave only negative results since the *d*-tartrates of *p*-tolylhydrazine⁴ (Fig. 11) and benzylphenylhydrazine⁵ (Fig. 12) could not be resolved. Jones and Millington⁶ using *d*-camphor-10-sulfonic

³ Wedekind and Klatte, *Ber.*, **60**, 2325 (1927).

⁴ Kraft, *Ber.*, **23**, 2780 (1890).

⁵ Behrend and König, *Ann.*, **263**, 184 (1891).

⁶ Jones and Millington, *Proc. Cambridge Phil. Soc.* **12**, 489 (1904).

acid in place of tartaric acid, repeated the attempt to resolve benzylphenylhydrazine, without success. They also prepared methylethylanilinesulfonic acid (Fig. 13) which could not be resolved with brucine. Meisenheimer ⁷ and co-workers were unable to resolve N-phenyl-N-*p*-tolylanthranilic acid (Fig. 14) and N-phenyl-N- α -naphthylanthranilic acid (Fig. 15) into their antipodes through the strychnine, brucine, morphine, and quinine salts.

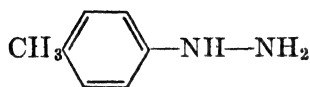


FIG. 11

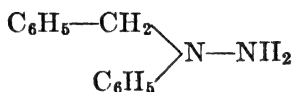


FIG. 12

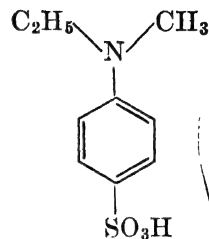


FIG. 13

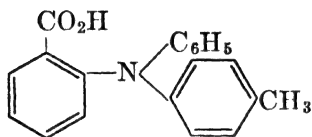


FIG. 14

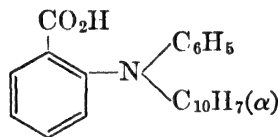


FIG. 15

All the sulfonium salts which had been resolved contained the $-\text{CH}_2\text{CO}-$ grouping, and as a consequence Meisenheimer ⁷ and co-workers prepared a number of amines of the type $R'R''\text{NCH}_2\text{COR}$ in hopes that they would be resolvable. However, the *d*-3-bromocamphor-8-sulfonic acid salts of N-methyl-N-ethylacetonylamine (Fig. 16),

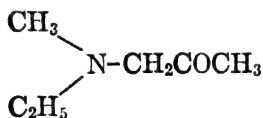


FIG. 16

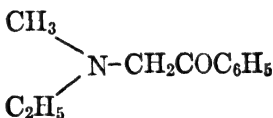


FIG. 17

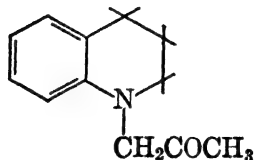


FIG. 18

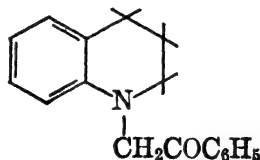


FIG. 19

N-methyl-N-ethylphenacylamine (Fig. 17), N-acetonyltetrahydroquinoline (Fig. 18), and N-phenacyltetrahydroquinoline (Fig. 19) gave completely negative results.

⁷ Meisenheimer, Angermann, Finn, and Vieweg, *Ber.*, **57**, 1745 (1924).

By analogy to the oximes, Denner⁸ believed that unsymmetrical hydroxylamines of this type would be capable of resolution. His endeavors to prepare active methylethylhydroxylamine (Fig. 20), methylbenzylhydroxylamine (Fig. 21), or methylbenzyloxy-*p*-anilinesulfonic acid (Fig. 22) were not successful.

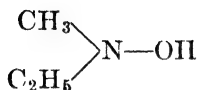


FIG. 20

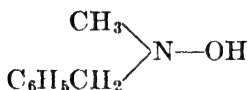


FIG. 21

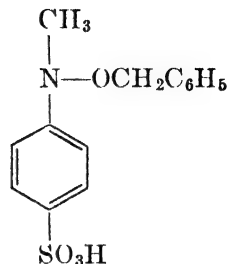


FIG. 22

Kipping and Salway⁹ introduced still another modification in the hope of getting some evidence for the existence of an optically active trivalent nitrogen atom. By using *dl*-methylbenzylacetyl chloride (Fig. 23) and condensing it with primary and secondary amines, they hoped to be able to separate the two diastereoisomers that would result (Fig. 24). The amides thus investigated were those prepared from methyl-

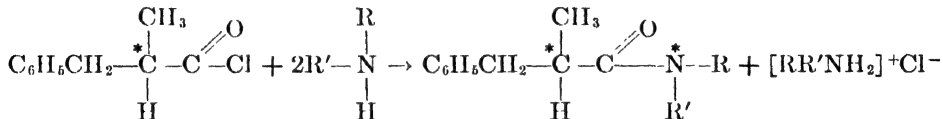


FIG. 23

FIG. 24

aniline, *p*-toluidine, benzyaniline, and phenylhydrazine. In no case were the investigators able to isolate the two forms. Frerejacque,¹⁰ using *d*-camphor-3-sulfonyl chloride in place of the *dl*-methylbenzylacetyl chloride, attempted the same sort of separation by preparing the amides of ethylaniline, and *o*- and *p*-toluidines, but no isomers could be isolated.

Inspection of the formulas of 2-methyldihydroindole (Fig. 25), 6-methyltetrahydroquinoline (Fig. 26), tetrahydroquinoline (Fig. 27),

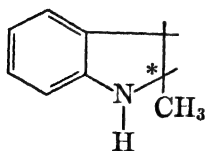


FIG. 25

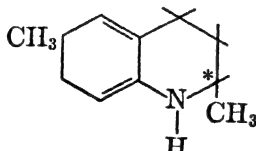


FIG. 26

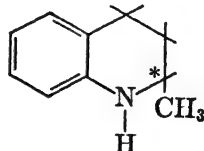


FIG. 27

⁸ Denner, Dissertation, Tübingen (1930).

⁹ Kipping and Salway, *J. Chem. Soc.*, **85**, 438 (1904).

¹⁰ Frerejacque, *Compt. rend.*, **187**, 894 (1928); *Ann. chim.*, **14**, 207 (1930).

and their acyl derivatives shows that they contain an asymmetric carbon atom, and also an "asymmetric" nitrogen atom. Two racemic forms or four optical isomers should exist. The fractional crystallization of the *d*-camphor-10-sulfonic acid and *d*-3-bromocamphor-8-sulfonic acid salts was studied by Pope,¹¹ and found to result in the production of *two* active forms only, which are due to the asymmetric carbon atom.

Hayashi¹² prepared a compound (Fig. 28) in which all three valences of the nitrogen atom were tied up in a complex ring system. Attempts to resolve this compound were unsuccessful.

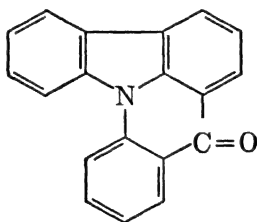


FIG. 28

Groth and Holmberg¹³ prepared 2-thion-4-methylthiazoline-3-acetic acid (Fig. 29), but could not resolve it with *d*-phenylethylamine

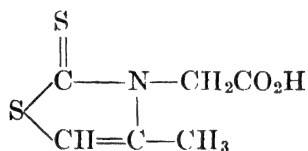


FIG. 29

Stewart and Allen¹⁴ studied the resolution of tertiary amines at very low temperatures, but were unable to resolve ethylbenzylaniline with either *d*-camphorsulfonic acid or *d*-bromocamphorsulfonic acid at -78°C .

If the configuration of the molecule could be fixed, then resolution should be successful. The possibility that heavy negative groups, such as acyl or sulfonyl, would be less mobile than alkyl or aryl groups led Schreiber and Shriner¹⁵ to prepare the following unsymmetrically substituted *p*-phenylenediamine derivatives (Figs. 30, 31, and 32) and to study their resolution by means of *d*-camphor-10-sulfonic acid. In

¹¹ Pope and Clark, *J. Chem. Soc.*, **85**, 1330 (1904); Pope and Beck, *ibid.*, **91**, 458 (1907); Pope and Read, *ibid.*, **97**, 2199 (1910).

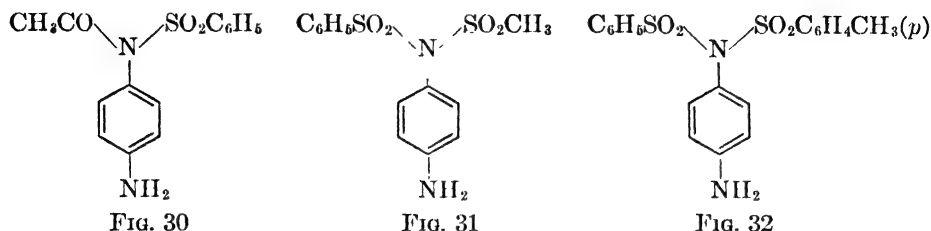
¹² Hayashi, *Bull. Inst. Phys. Chem. Research (Tokyo)*, **9**, 970 (1930).

¹³ Groth and Holmberg, *Ber.*, **56**, 289 (1907).

¹⁴ Stewart and Allen, *J. Am. Chem. Soc.*, **54**, 4027 (1932).

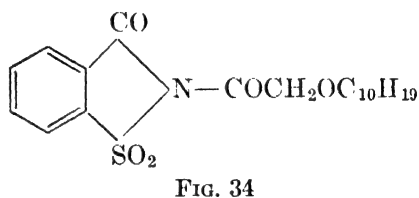
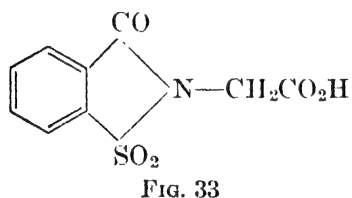
¹⁵ Schreiber and Shriner, *ibid.*, **57**, 1306, 1445, 1896 (1935).

these compounds, salt formation takes place at the free *p*-amino group, and hence salt formation should not disturb the spatial arrangement about the tertiary nitrogen atom.



These salts were shown by analysis to consist of one mole of the base and one mole of the *d*-camphor-10-sulfonic acid. Upon studying the optical rotation of these salts it was discovered that methanol, ethanol, or chloroform solutions of these compounds exhibited *mutarotation*. This mutarotation (*cf.* p. 307) was shown to be due to a reaction of the primary amino group with the keto group of the *d*-camphor-10-sulfonic acid forming ketimines. Decomposition of the salts or ketimines always gave optically inactive products.

Fractional crystallization of the brucine salts of the substituted imide, Fig. 33, also failed to yield diastereoisomeric salts. The compound, Fig. 34, *N*-(*l*-menthoxyacetyl)-saccharin, contains three acyl groups



attached to the nitrogen. Fractional crystallization failed to yield diastereoisomers.

From recent studies on the resonance (p. 1950) of electrons between different atoms in a compound, Pauling¹⁶ has suggested that compounds having phenyl or acyl groups attached to nitrogen may not be resolvable, owing to resonance between the unshared pair of electrons on the nitrogen and the adjacent unsaturated groupings (Fig. 35).

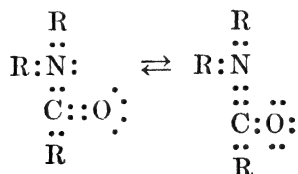


FIG. 35

¹⁶ Pauling, *J. Chem. Phys.*, **1**, 606 (1933).

Mumm and Herrendörfer¹⁷ reported the isolation of two racemic forms of the dicyanodihydroquinoline to which were assigned the structures shown in Figs. 36 and 37. The compounds were produced by the action of cyanogen bromide and hydrogen cyanide on quinoline.

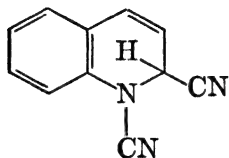


FIG. 36

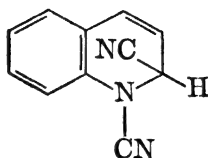


FIG. 37

Pairs of isomerides were also obtained¹⁸ with 3-methylquinoline, 6-methylquinoline, 6-methoxyquinoline, and β -naphthaquinoline. Both the isomerides of Figs. 36 and 37 gave quinoline-2-carboxylic acid upon treatment with hydrochloric acid at 150°. Both isomers yielded 2-cyanoquinoline by the action of iodine in chloroform in the presence of sodium acetate. Iodine in alcoholic pyridine solution converted them into the same apocyanine dye (Fig. 38).

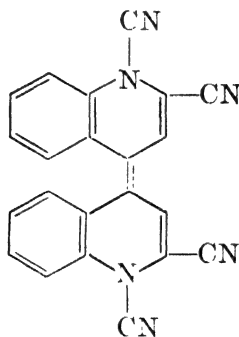


FIG. 38

The continued persistence in the attempts to resolve a trivalent nitrogen compound, in view of the astonishing number of failures, can be accounted for only by the convincing, indirect evidence for the tetrahedral structure of the nitrogen atom. This evidence may be summarized briefly.

The tetrahedral structure of the nitrogen atom is indicated by the classes of compounds known as nitriles (Fig. 39) and the diazonium salts (Fig. 40). Since the tetrahedral structure for the carbon atom is well established, the ease of formation and stability of the nitriles in which three valencies of carbon are attached to three valencies of nitrogen is indicative of a tetrahedral structure for nitrogen rather than a planar one.

¹⁷ Mumm and Herrendörfer, *Ber.*, **47**, 758 (1914).

¹⁸ Mumm, Ludwig, Lu, and Radenhausen, *Ann.*, **514**, 34 (1934).

In the second place, it is well known that a nitrogen atom may be substituted for a $=\text{CH}-$ group, or an $-\text{NH}-$ group for a $-\text{CH}_2-$

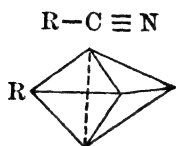


FIG. 39

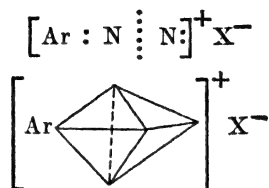


FIG. 40

radical. Such substitution may even produce an increase in the relative stability of the analogous compounds. This is well demonstrated by comparing benzene and pyridine (Fig. 41), hexahydrobenzene and piperidine (Fig. 42), cyclopentadiene and pyrrole (Fig. 43). It appears to be logical that, if a tetrahedral group is replaced by a second group without a decided change in stability of the resulting compound, the second group must be tetrahedral or nearly so. Such compounds as the tetrazoles, Fig. 44, could not possibly form if the bonds of the ni-

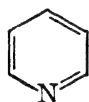


FIG. 41

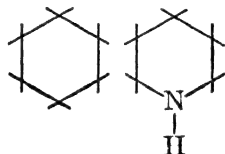


FIG. 42

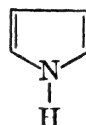
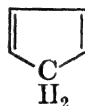


FIG. 43

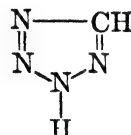


FIG. 44

trogen atom all lie in the same plane. Recently it has been shown from x-ray data that the nitrogen atom in hexamethylenetetramine (Fig. 45) lies at the peak of a three-sided pyramid with a carbon atom at each corner of the base. The presence of the nitrogen atom in a complex ring system of the quinuclidine type (Fig. 46), or in such compounds as those shown in Fig. 47 and Fig. 28, makes it almost imperative

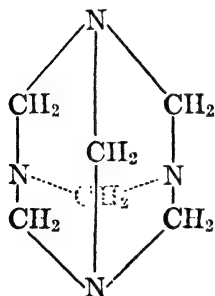


FIG. 45

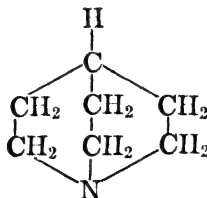


FIG. 46

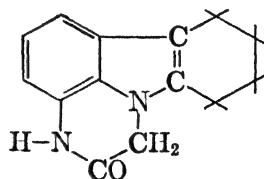


FIG. 47

that the nitrogen atom be tetrahedral, since these compounds are very stable.

In contrast to the fact that no trivalent nitrogen compounds have been resolved are the numerous pairs of *syn* and *anti* oximes (Figs. 48 and 49) which can be explained only on the basis of a tetrahedral nitrogen atom. The resolution by Mills¹⁹ and his students of the compounds shown in Figs. 50, 51, 52, 53, and 54 is further proof that the three valencies of the nitrogen are not coplanar. The oxime, Fig. 50, would

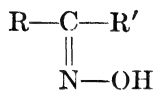


FIG. 48

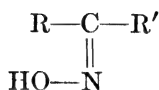


FIG. 49

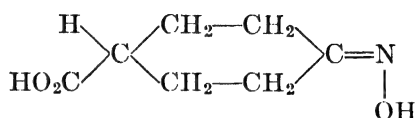


FIG. 50

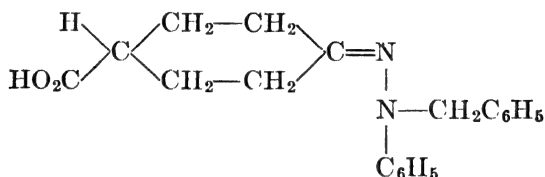


FIG. 51

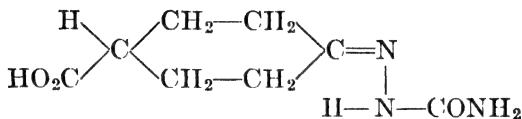


FIG. 52

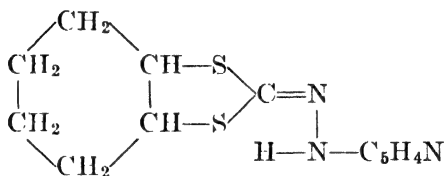


FIG. 53

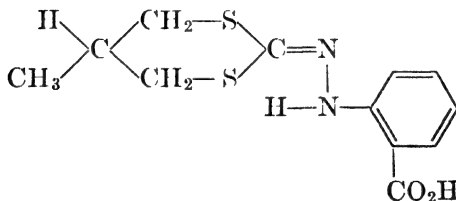


FIG. 54

possess a plane of symmetry if the hydroxyl group extended straight out coaxially with the carbon-double-bonded-nitrogen linkage.

Consideration of the physical properties of ammonia, the amines, and other trivalent nitrogen compounds also points rather conclusively

¹⁹ Mills and Bain, *J. Chem. Soc.*, **97**, 1866 (1910); *ibid.*, **105**, 64 (1914); Mills and Saunders, *ibid.*, 537 (1931); Mills and Schindler, *ibid.*, **123**, 312 (1923).

to a non-planar arrangement of the nitrogen valencies and supports the tetrahedral structure.²⁰ Ammonia and the amines possess considerable dipole moments which are most readily explained on a tetrahedral basis. The principal moments of inertia of the ammonia molecule have been calculated from studies on its infra-red absorption spectrum, and these data indicate a tetrahedral shape. The exact dimensions of the ammonia molecule have been determined:²¹ the perpendicular distance from the nitrogen to the center of the face is 0.34 to 0.36 Å, the length of the N-H distance is 1.01 Å, and the distance between any two hydrogen atoms is 1.64 Å; the angle between the nitrogen valencies is 108 to 109.5°. Studies on the crystal structure of solid ammonia by x-rays²² and theoretical calculations²³ point to a tetrahedral arrangement. Also, the dipole-moment studies²⁴ and observations on the vibration spectra²⁵ of hydrazine indicate a non-planar arrangement of the valencies of the nitrogen atoms.

Since all the foregoing chemical and physical evidence points so conclusively to a non-planar arrangement of the valencies of trivalent nitrogen compounds, it seems that the failure to resolve suitably substituted derivatives of ammonia must be due to some particularly easy mode of racemization by a mechanism which requires very little energy.

Meisenheimer²⁶ pointed out that passage of the nitrogen atom of a compound $\text{NRR}'\text{R}''$ through the plane of the three substituents, R, R', and R'', would produce the enantiomorphic form. If rapid vibration between the two positions shown in Figs. 55 and 56 takes place, only

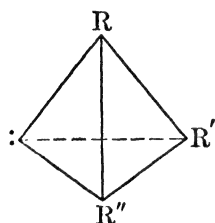
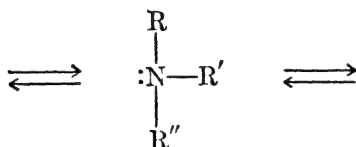


Fig. 55



Transient planar position

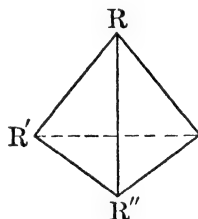


Fig. 56

²⁰ In many papers, trivalent nitrogen compounds are designated as pyramidal, the unshared pair of electrons being disregarded. This is merely a matter of nomenclature; the viewpoints are identical. Cf. "Organic Chemistry of Nitrogen," Sidgwick, Taylor, and Baker, Oxford Univ. Press (1937), p. 38.

²¹ Migeotte and Barker, *Phys. Rev.*, **50**, 418 (1936); Wright and Randall, *ibid.*, **44**, 391 (1933).

²² Mark and Pohland, *Z. Krist.*, **61**, 532 (1925); de Smedt, *Bull. sci. acad. roy Belg.*, [5] **11**, 655 (1925).

²³ Penney and Sutherland, *J. Chem. Phys.*, **2**, 492 (1934).

²⁴ Audrieth, Nespital, and Ulich, *J. Am. Chem. Soc.*, **55**, 673 (1933).

²⁵ Imanishi, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **16**, 1 (1931); Sutherland *Nature*, **126**, 916 (1930).

²⁶ Meisenheimer, Angermann, Finn, and Vieweg, *Ber.*, **57**, 1747 (1924).

racemic modifications would result. A side view of this vibrational process is shown in Figs. 57, 58, and 59 in which the dots represent the three substituents on one face of the tetrahedron.

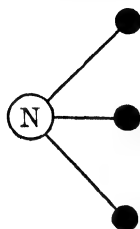


FIG. 57

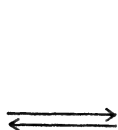


FIG. 58

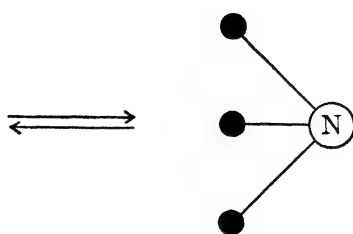


FIG. 59

Such a vibration of the nitrogen atom offers an explanation of some of the doublet structure of many of the lines in the absorption spectra of ammonia.²⁷ Wall and Glockler²⁸ have found that the theoretical and calculated values for the doublet separations for the parallel type frequencies of mono-, di-, and trideutero ammonias agree very well on the basis of such a vibration of the nitrogen atom.

Calculations of the energy required to cause the nitrogen atom to pass through the plane of the hydrogen atoms have been made. The values^{28, 29, 30} obtained range from a low of 6 kcal.²⁹ to a high of 11 kcal.³⁰ per mole. For resolution to be possible at room temperature ΔE should be greater than 25 kcal. per mole. It thus appears that the resolution of an amine of the type $\text{NRR}'\text{R}''$ is impossible at room temperature. On the other hand, the activation energy for N-methylethyleneimine was calculated to be 38 kcal. per mole, and thus a resolution of a properly substituted ethyleneimine appears possible.³⁰ The resolution of compounds of the types shown in Figs. 60, 61, and 62

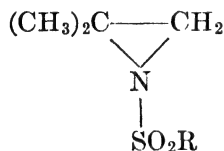


FIG. 60

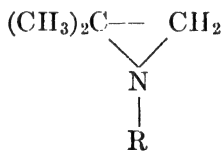


FIG. 61

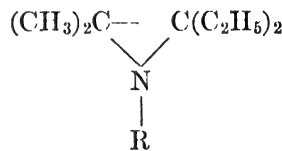


FIG. 62

should be possible; a number of investigations³¹ have been carried out on the synthesis and resolution of such compounds, but up to the present

²⁷ Barker, *Phys. Rev.*, **33**, 684 (1929); Badger, *ibid.*, **35**, 1038 (1930).

²⁸ Wall and Glockler, *J. Chem. Phys.*, **5**, 314 (1937).

²⁹ Manning, *ibid.*, **3**, 136 (1935).

³⁰ Kincaid and Henriques, *J. Am. Chem. Soc.*, **62**, 1474 (1940).

³¹ Meisenheimer and Chou, *Ann.*, **539**, 70 (1939); Adams and Cairns, *J. Am. Chem. Soc.*, **61**, 2464 (1939); Mole and Turner, *Chemistry & Industry*, 582 (1929); Maitland *Ann. Repts. Chem. Soc. (London)*, **36**, 243 (1939).

time no positive results have been obtained. Difficulties are experienced in synthesizing the properly substituted ethylencimines and also in obtaining crystalline derivatives suitable for separation.

Quaternary Ammonium Salts. It is well established that in ammonium salts, such as ammonium chloride, the nitrogen is attached to the four hydrogen atoms forming the positive ammonium ion and the chlorine is present as the negative chloride ion with no direct union between the two except the electrostatic charge (Fig. 63).

The fact that this fifth valence of nitrogen is an electrovalence and that the other four are covalencies was shown by Schlenk,³² who prepared the two compounds shown in Figs. 64 and 65 and found that these

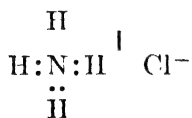


FIG. 63

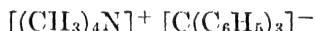


FIG. 64

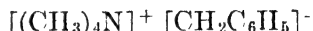
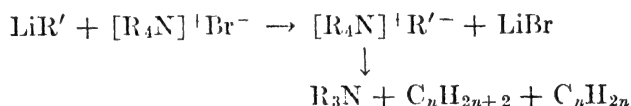


FIG. 65

compounds containing only alkyl groups behaved in a manner analogous to other ammonium salts when dissolved in a suitable solvent. They conducted the electric current and showed all the evidences of ionization.

Hager and Marvel³³ also demonstrated that five alkyl groups could not be similarly attached to a nitrogen atom. The reaction of lithium alkyls with quaternary ammonium halides produced unstable penta-alkyl nitrogen compounds which immediately decomposed into hydrocarbons and tertiary amines, as expressed by the following type reaction:



In no case was the R' group furnished by the alkyllithium ever found attached to the nitrogen of the tertiary amine in the final product. Meisenheimer³⁴ also succeeded in preparing the two isomeric compounds shown in Fig. 66 and Fig. 67 which underwent decomposition in the manner shown.

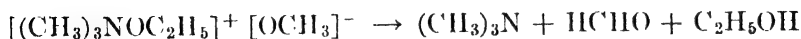


FIG. 66

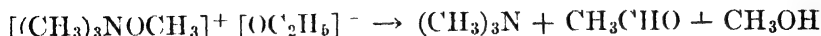


FIG. 67

³² Schlenk and Holtz, *Ber.*, **49**, 603 (1916); **50**, 274 (1917).

³³ Hager and Marvel, *J. Am. Chem. Soc.*, **48**, 2689 (1926).

³⁴ Meisenheimer, *Ann.*, **397**, 273 (1913); Henze, *Ber.*, **70**, 1270 (1937).

If the five valencies of the nitrogen were equivalent no isomers should have been obtained and the decomposition products should have been identical.

With the recognition of the fact that the ammonium ion contains only four groups directly attached to the nitrogen atom, it is clear that quarternary ammonium compounds with four different groups attached (Fig. 68) should exhibit optical isomerism. The nitrogen atom of the ammonium ion should, therefore, be represented as a tetrahedron, shown in Fig. 69. It is evident that the negative ion plays no part in determining the asymmetry of the molecule.

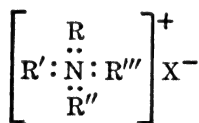


FIG. 68

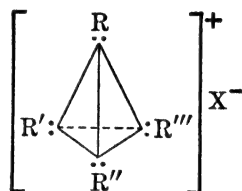


FIG. 69

In 1891, Le Bel³⁵ inoculated a solution of methylethylisopropylisobutylammonium chloride (Fig. 70) with *Penicillium glaucum* and found that after a time the solution exhibited a specific rotation of -7 to -8° , indicating that the mold had destroyed some of the *dextro*-isomer.

In 1899, Pope and Peachey³⁶ succeeded in obtaining both the *d*- and *l*-forms of methylallylbenzylphenylammonium iodide (Fig. 71).

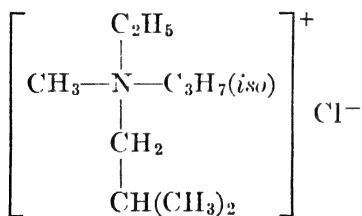


FIG. 70

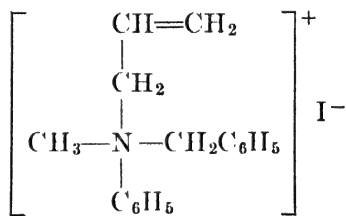


FIG. 71

The separation was accomplished by crystallization of the *d*- α -bromo- π -camphorsulfonates and decomposition of the two salts by potassium iodide. Wedekind³⁷ resolved the cyclic compound shown in Fig. 72, thus demonstrating that two of the valencies of the nitrogen could be

³⁵ Le Bel, *Compt. rend.*, **112**, 724 (1891); *J. chim. phys.*, **2**, 340 (1904).

³⁶ Pope and Peachey, *J. Chem. Soc.*, **75**, 1127 (1899); Pope and Harvey, *ibid.*, **79**, 834 (1901).

³⁷ Wedekind and Wedekind, *Ber.*, **40**, 4450 (1927).

members of a ring. However, compounds of the structure shown in Fig. 73 could not be resolved, and construction of the model of this molecule shows that the R group is in the plane of the two rings; this molecule, therefore, possesses a plane of symmetry and should be non-

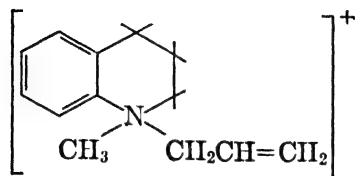


FIG. 72

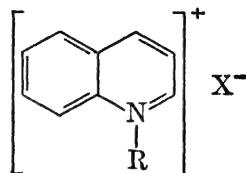


FIG. 73

resolvable. Many other quaternary ammonium salts have been resolved, and there are now many examples of active quaternary ammonium ions.³⁸ Some of these are the following (Figs. 74, 75, and 76), where R = C₂H₅, *n*-C₃H₇, *iso*-C₃H₇, *n*-C₄H₉, *iso*-C₄H₉, or *iso*-C₅H₁₁:

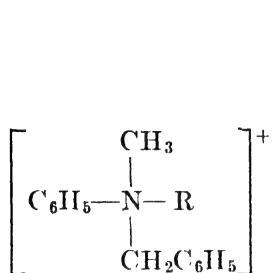


FIG. 74

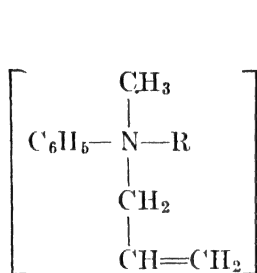


FIG. 75

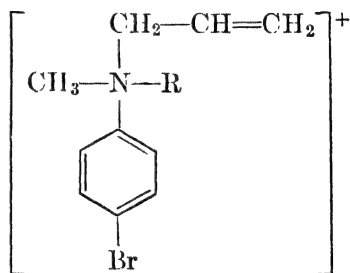


FIG. 76

Wedekind³⁹ obtained two forms of the molecule shown in Fig. 77 corresponding to the *meso* and racemic forms.

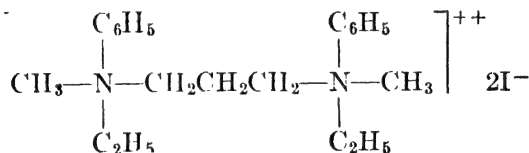


FIG. 77

Unique proof that nitrogen in ammonium compounds is tetrahedral was furnished by Mills and Warren^{40a} in 1925 when they succeeded in preparing and resolving 4-phenyl-4'-carbethoxy-*bis*-piperidin-

³⁸ Jones, *J. Chem. Soc.*, **85**, 223 (1904); Thomas and Jones, *ibid.*, **89**, 280 (1906); Jones and Hill, *ibid.*, **93**, 295 (1908); Wedekind and Frölich, *Ber.*, **38**, 3438 (1905); **40**, 1001 (1907).

³⁹ Wedekind and Wedekind, *Ber.*, **43**, 2707 (1910); Wedekind and Goost, *Ber.*, **49**, 942 (1916).

^{40a} Mills and Warren, *J. Chem. Soc.*, **127**, 2507 (1925).

in which a tetrahedral carbon atom occupies the position common to both rings.

The preparation of the two quaternary salts shown in Figs. 79a and 79b has been reported by J. R. Johnson.^{40b} The first compound (Fig.

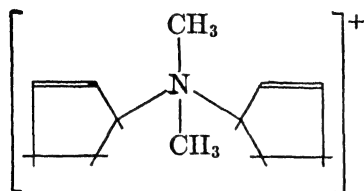


FIG. 79a

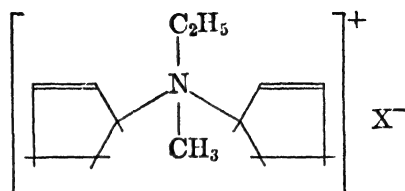


FIG. 79b

79a) contains two similar asymmetric carbon atoms and hence exists in a *dl* and a *meso* form, both of which were isolated.

The second quaternary salt (Fig. 79b) contains a pseudoasymmetric nitrogen atom and hence this salt should exist in one racemic modification and *two meso* forms. All three forms were isolated.

Amine Oxides. These compounds, which have the general formula R_3NO , may be prepared by two methods. The direct action of hydrogen peroxide on a tertiary amine results in the formation of a hydrate (Fig. 80) in the solution. Evaporation of the solution yields crystals of the amine oxide dihydrate, $R_3NO \cdot 2H_2O$, which, upon gentle heating in a vacuum, loses its water of crystallization and combination, and yields the anhydrous amine oxide shown in Fig. 81.

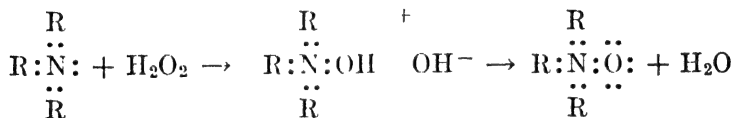


FIG. 80

FIG. 81

A second method of preparation is by the condensation of a disubstituted hydroxylamine with an alkyl iodide. The quaternary iodide is treated with silver hydroxide and a hydrate is produced which upon drying *in vacuo* gives the amine oxide. The equations at the top of p. 418 summarize the reactions.

These amine oxides and especially their hydrates are crystalline solids readily soluble in water. Such solutions possess a rather low conductivity as compared with the quaternary ammonium hydroxides.

The structure shown in Fig. 82 represents the oxygen as held to the nitrogen by a semi-polar linkage: i.e., by a pair of electrons furnished by

^{40b} Johnson, Eighth National Organic Chemistry Symposium, St. Louis, Mo. (1939).

the nitrogen atom. The evidence in favor of such a structure is based on a determination of dipole moments, parachors, and especially on Meisenheimer's observation that amine oxides containing three different R

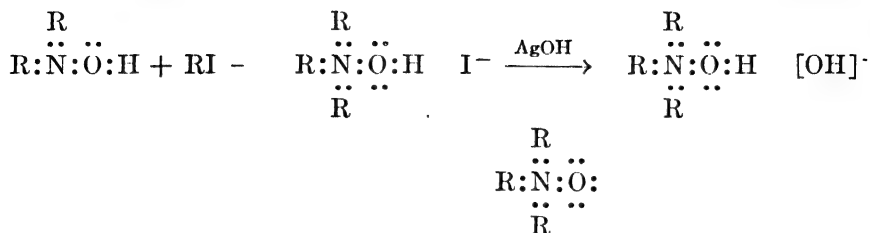


FIG. 82

groups are capable of being resolved into optical enantiomorphs. The spatial formula for such molecules is shown in Fig. 83, in which the nitrogen atom is represented by the tetrahedron. The amine oxides form

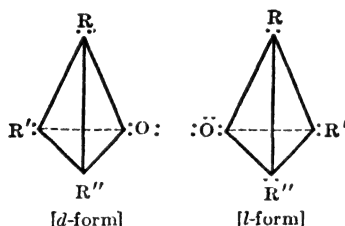
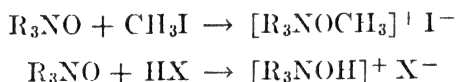
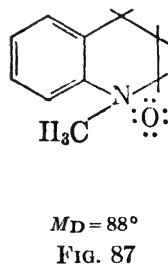
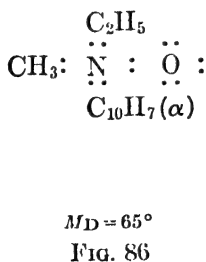
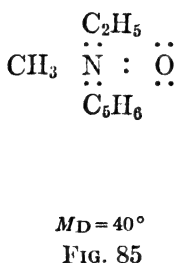
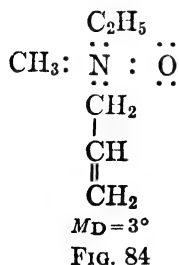


FIG. 83

addition compounds with alkyl halides and acids, as indicated by the equations:



Using the last type of reaction Meisenheimer^{40c} formed salts of asymmetrical amine oxides with *d*-bromocamphorsulfonic acid, separated the diastereoisomeric salts, and regenerated the amine oxides by means of alkali. In this manner, the following amine oxides were resolved:



^{40c} Meisenheimer, *Ber.*, **41**, 3966 (1908); *Ann.*, **385**, 117 (1911); **428**, 252 (1922); **449** 191 (1926).

It is noteworthy that the molecular rotations become higher as the differences between the groups become greater (Figs. 84, 85, 86, and 87).

Sulfur. *Sulfonium Salts.* The reaction between sulfides and an active halogen compound produces sulfonium salts with the structure shown in Fig. 88. If the sulfur possesses a tetrahedral distribution of

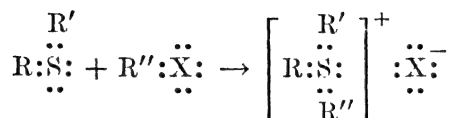


FIG. 88

its valencies and the unshared pair of electrons acts as the fourth group, then optical isomers are possible, provided that the R groups are different.

The resolution of sulfur compounds of this type was accomplished simultaneously by Pope and Peachey⁴¹ and by Smiles⁴² in 1900. The addition of bromoacetic acid to methyl ethyl sulfide yielded methyl-ethylcarboxymethylsulfonium bromide (Fig. 89).

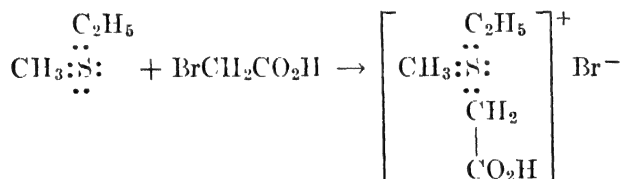


FIG. 89

This bromide was treated with silver *d*-camphorsulfonate, the silver bromide was removed, and the resulting *d*-camphorsulfonate (Fig. 90)

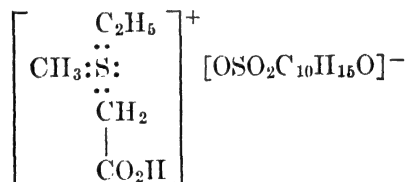


FIG. 90

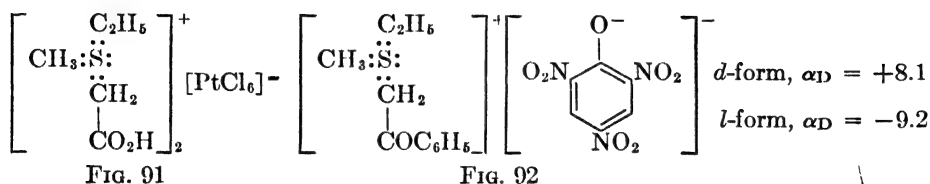
was recrystallized 40–50 times from an alcohol-ether mixture. The less soluble salt proved to be the *d*-methylethylcarboxymethylsulfonium-*d*-camphorsulfonate which possessed a molecular rotation of $M_D = +68^\circ$. The rotation of the camphorsulfonate ion is $+51.7^\circ$, which leaves a

⁴¹ Pope and Peachey, *J. Chem. Soc.*, **77**, 1072 (1900).

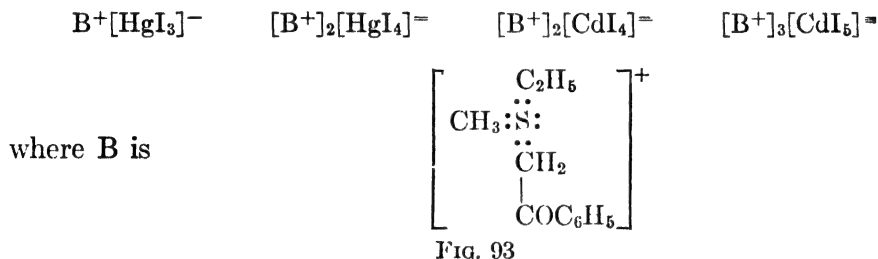
⁴² Smiles, *ibid.*, **77**, 1174 (1900).

rotation of $+16.3^\circ$ for the optically active *d*-sulfonium ion. Treatment with chloroplatinic acid removed the camphorsulfonate ion and gave the chloroplatinate (Fig. 91) which had a specific rotation of $+4.5^\circ$ and M_D of $+30.2^\circ$.

By a similar procedure, Smiles⁴² obtained the picrates of the two active forms of methylethylphenacylsulfonium ions (Fig. 92) by crystallization of the *d*-bromocamphorsulfonates.

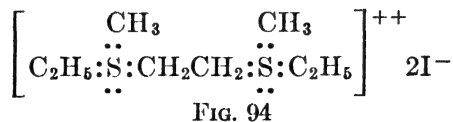


The mercuritriiodide and tetraiodide of the phenacylmethylethylsulfonium salt have been obtained in optically active forms and also the cadmiiodides.⁴³ Their formulas (Fig. 93) may be represented as follows:



An attempt by Smiles⁴⁴ to secure optically active sulfonium compounds by the combination of methyl ethyl sulfide with *l*-menthyl α -bromoacetate failed since the two diastereoisomeric methylethylthetine bromide *l*-menthyl esters were produced in equal amounts.

Wedekind⁴⁵ obtained two forms (m.p. 123° and 154°) of the compound shown in Fig. 94 which correspond to *meso* and racemic forms.



This compound has two similar sulfur atoms acting as centers of asymmetry.

⁴³ Balfe, Kenyon, and Phillips, *ibid.*, 2554 (1930).

⁴⁴ Smiles, *ibid.*, 87, 450 (1905).

⁴⁵ Wedekind, *Ber.*, 58, 2510 (1925).

These optically active sulfonium ions of the general formula in Fig. 95 are electronically similar to the negative carbanions, Fig. 96, discussed

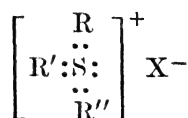


FIG. 95

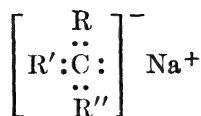


FIG. 96

on p. 388. In each case one corner of the tetrahedron is occupied by an unshared pair of electrons.

Sulfinic Esters and Sulfoxides. The resolution of sulfinic esters of the general formula RSOOR was of great importance, since it was the first case of the existence of optical isomers in a *neutral* compound containing *only three* groups attached to the central atom. In 1925 Phillips⁴⁶ digested together the *p*-toluenesulfinate of *l*-2-octanol and ethyl alcohol. A partial ester interchange took place, and by fractional distillation the optically active ethyl ester was obtained. The only structure capable of explaining the optical activity of this ester is that shown in Fig. 97 which must replace the old formula shown in Fig. 98.

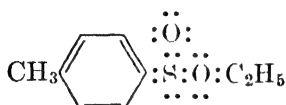


FIG. 97

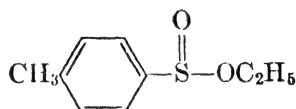


FIG. 98

It is clear that in Fig. 97 the sulfur is asymmetric, whereas in Fig. 98 no asymmetry is indicated. In the same way, the optically active *n*-butyl ester of *p*-toluenesulfinic acid was obtained. The process was also successful if *l*-menthyl *p*-toluenesulfinate was used as the starting material.

The fact that sulfur compounds of this general structure may exist in optically active forms was even more strikingly confirmed by the resolution⁴⁷ of the three sulfoxides shown in Figs. 99, 100, and 101.

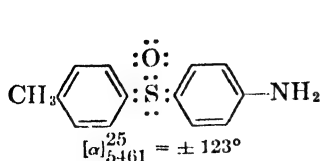


FIG. 99

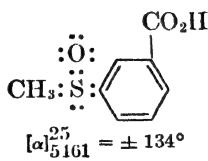


FIG. 100

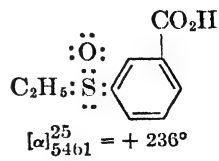


FIG. 101

⁴⁶ Phillips, *J. Chem. Soc.*, **127**, 2552 (1925).

⁴⁷ Harrison, Kenyon, and Phillips, *ibid.*, 2079 (1926).

The disulfoxide shown in Fig. 102 contains two similar asymmetric

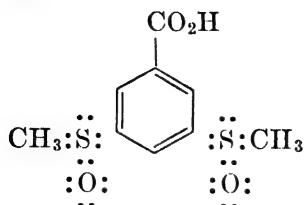


FIG. 102

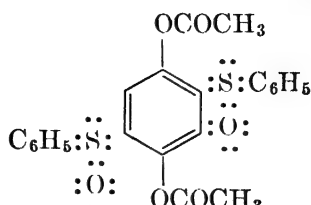


FIG. 103

sulfur atoms and hence should exist in a *meso* and racemic modification. This prediction was realized experimentally by Bell and Bennett,⁴⁸ who obtained the two isomers. One of them was resolved; the other resisted resolution. The two diastereoisomers of Fig. 103 were obtained by Maclean and Adams.⁴⁹

The electronic formulas shown above for the sulfinic esters and sulf-oxides represent the oxygen attached to the sulfur as a semi-polar oxygen. This linkage of the oxygen to the sulfur by a single pair of electrons is supported not only by the above stereochemical evidence, but also by measurements of the dipole moments of sulfoxides.

Sulfilimines. By the condensation of chloramine-T with *m*-carboxyphenylmethyl sulfide a compound was obtained known as a sulfilimine, usually represented by the formula shown in Fig. 104. This compound

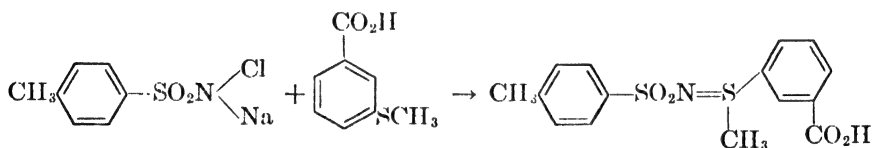
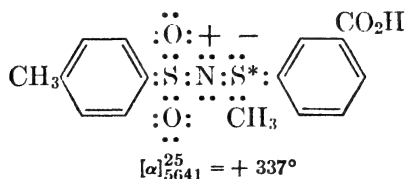


FIG. 104

was resolved into *d*- and *l*-forms by means of the brucine and cinchonine salts. The conventional structure above indicates no reason for the asymmetry. Clarke, Kenyon, and Phillips⁵⁰ point out that, if the nitrogen-sulfur linkage is semi-polar like that of the sulfur-oxygen linkage in Fig. 99, then the sulfur atom is asymmetric and the existence of optical isomers becomes obvious. Such a structure is shown in Fig. 105, in



$$[\alpha]_{5641}^{25} = + 337^{\circ}$$

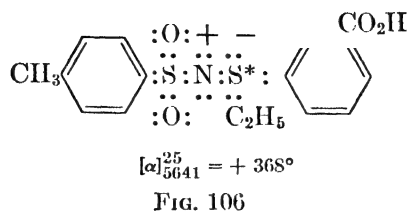
FIG. 105

⁴⁸ Bell and Bennett, *ibid.*, 1 (1930).

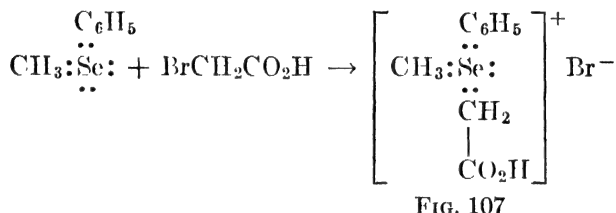
⁴⁹ Maclean and Adams, *J. Am. Chem. Soc.*, **55**, 4681 (1933).

⁵⁰ Clarke, Kenyon, and Phillips, *J. Chem. Soc.*, 188 (1927).

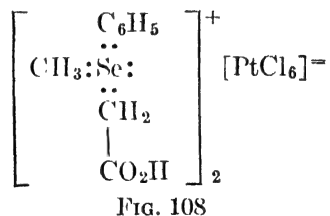
which the asymmetric sulfur atom is indicated by an asterisk. The analogous ethyl derivative was also resolved (Fig. 106).



Selenium. The selenonium salts behave in a manner quite analogous to the sulfonium salts. Thus, methyl phenyl selenide combines with bromoacetic acid to give methylphenylcarboxymethylselenonium bromide (Fig. 107).



In this compound the selenium is asymmetric and should exhibit optical isomerism. By treatment with silver *d*-bromocamphorsulfonate, Pope and Neville⁵¹ succeeded in obtaining the bromocamphorsulfonates which were separated by repeated crystallization. The bromocamphorsulfonates were converted to the chloroplatinates (Fig. 108) which had M_D of $+55.0$ and -54.3° , respectively.



Attempts to resolve⁵² selenoxides of the structures shown in Figs. 109, 110, and 111 failed, although it is to be expected that the resolution of this type of selenium derivative should be possible if the right conditions were obtained.

⁵¹ Pope and Neville, *ibid.*, **81**, 1552 (1902).

⁵² Gaythwaite, Kenyon, and Phillips, *ibid.*, 2280, 2287 (1928); Edwards, Gaythwaite Kenyon, and Phillips, *ibid.*, 2293 (1928).

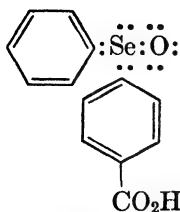


FIG. 109

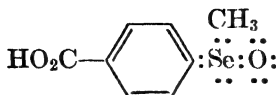


FIG. 110

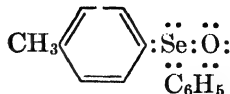


FIG. 111

Tellurium. The quadrivalent derivatives of this element were for some time cited as the outstanding examples of the presence of four valencies in one plane. Vernon⁵³ reported the isolation of two geometrical isomers corresponding to Figs. 112 and 113, but recent investigations by Drew⁵⁴ and by Lowry and Gilbert have shown that no such isomers exist, and that the compounds obtained were molecularly different. In 1929, Lowry and Gilbert⁵⁵ isolated phenyl-*p*-tolylmethyltelluronium salts (Fig. 114) in optically active forms which had molecular rotations of about 70°. The compounds racemize readily, but the behavior of these telluronium salts indicates that they are very similar to the sulfonium and selenonium salts. The tellurium atom is hence tetra-

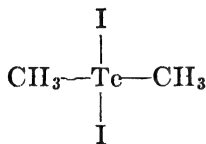


FIG. 112

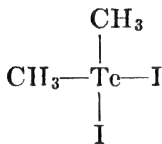


FIG. 113

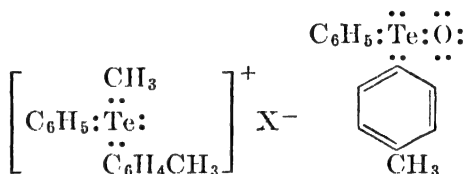


FIG. 114

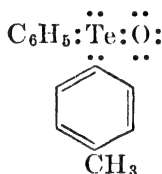


FIG. 115

hedral and not planar since no optical activity would be possible if the above structure were planar. Telluronium oxides (Fig. 115) have not as yet been split into optical enantiomorphs.

Tin. In 1900 Pope and Peachey⁵⁶ synthesized methylethyl-*n*-propylstannonium iodide (Fig. 116) by the following reactions:

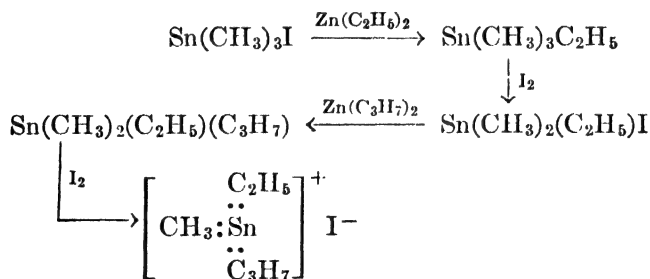


FIG. 116

⁵³ Vernon, *ibid.*, **117**, 86, 889 (1920); Knaggs and Vernon, *ibid.*, **119**, 105 (1921).

⁵⁴ Drew, *ibid.*, 560 (1929).

⁵⁵ Lowry and Gilbert, *ibid.*, 2867 (1929).

⁵⁶ Pope and Peachey, *Proc. Roy. Soc. (London)*, **16**, 42, 116 (1900).

The product was a yellow oil insoluble in water. When treated with silver *d*-camphorsulfonate a salt was obtained which had M_D of $+95^\circ$, thus indicating that the rotatory value of the methylethyl-*n*-propylstannonium radical was about $+45^\circ$. The salt was then converted back to the iodide which was an oil with M_D of $+23^\circ$. Hence, the tin compounds are analogous to the other optically active *onium* salts, and the tin atom is tetrahedral in these compounds. Only the *d*-form of the above salt could be obtained, since, on concentrating solutions of the *d*-camphorsulfonate salt, the *d*-methylethyl-*n*-propylstannonium *d*-camphorsulfonate was the less soluble and crystallized out of solution. The *l*-form in solution changed over to the *d*-form as evaporation of the mother liquor proceeded until the conversion was complete. Similar results were obtained with the stannonium salts of *d*-bromocamphorsulfonic acid.

Germanium. Schwarz and Lewinsohn⁵⁷ added germanium to the list of elements with tetrahedral asymmetry by the resolution of phenyl-ethylisopropylgermanium bromide (Fig. 117) through the *d*-bromocamphorsulfonate.

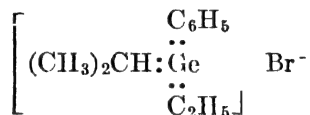


FIG. 117

Phosphorus. The investigations on the compounds of phosphorus have not been so numerous as those on the nitrogen compounds. Although unsymmetrical phosphines $\text{RR}'\text{R}''\text{P}$ and phosphonium compounds $[\text{RR}'\text{R}''\text{R}'''\text{P}]^+\text{X}^-$ should be resolvable, no optical isomers of these compounds are known. The action of alkali metal alkyls on quaternary phosphonium halides⁵⁸ shows that no pentaalkyl phosphorus compounds exist in which five equivalent valencies are attached to the phosphorus atom.

However, Meisenheimer⁵⁹ succeeded in resolving methylethylphenylphosphine oxide (Fig. 118) by means of *d*-bromocamphorsulfonic acid. Kipping⁶⁰ also obtained the two diastereoisomeric forms of phenyl- β -naphthylphosphoryl-*l*-menthylamide (Fig. 119).

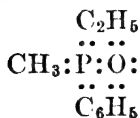


FIG. 118

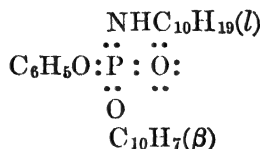


FIG. 119

⁵⁷ Schwarz and Lewinsohn, *Ber.*, **64**, 2352 (1931).

⁵⁸ Coffman and Marvel, *J. Am. Chem. Soc.*, **51**, 3496 (1929).

⁵⁹ Meisenheimer and Lichtenstadt, *Ber.*, **44**, 356 (1911).

⁶⁰ Kipping and Challenger, *J. Chem. Soc.*, **99**, 626 (1911).

The *meso* and racemic forms of ethyl triphenylmethylpyrophosphate (Fig. 120) have been obtained by Hatt.⁶¹ Both forms give the

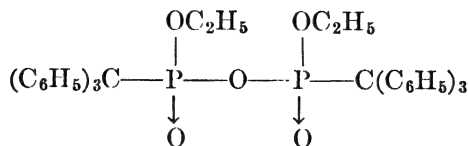


FIG. 120

same acid (Fig. 121) on hydrolysis, owing to ionization of the hydrogen atoms from the hydroxyl groups.

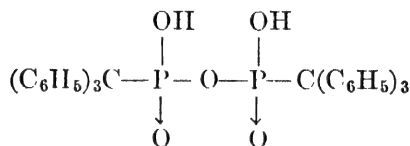
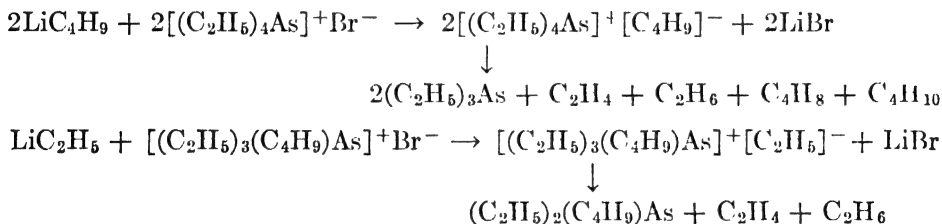


FIG. 121

Arsenic. The stereochemical configuration of arsenic compounds is in all probability similar to that of corresponding derivatives of nitrogen and phosphorus.

Investigations have shown that in arsonium compounds only four groups are directly linked to the arsenic and that the fifth valency is an electrovalency. Friedrich and Marvel⁶² studied reactions which might lead to isomeric products of the type $\text{R}_4\text{AsR}'$ and $\text{R}_3\text{R}'\text{AsR}$, as indicated by the following equations:



The pentaalkylarsines were very unstable and could not be isolated, but the fact that these two reactions gave entirely different decomposition products showed that the arsenic atom does not share five pairs of electrons with five alkyl groups. The alkyl group furnished by the lithium never appeared attached to the arsenic in the tertiary arsine.

Attempts to resolve arsonium compounds were for some time unsuccessful. Finally, in 1921, Burrows and Turner⁶³ succeeded in ob-

⁶¹ Hatt, *ibid.*, 776 (1934).

⁶² Friedrich and Marvel, *J. Am. Chem. Soc.*, **52**, 376 (1930).

⁶³ Burrows and Turner, *J. Chem. Soc.*, 426 (1931).

taining a solution of phenyl- α -naphthylbenzylmethylarsonium iodide (Fig. 122) which showed a slight *dextro* rotation. The arsonium compound was resolved through the use of *d*-bromocamphorsulfonic acid, and the molecular rotation of the salts indicated rather conclusively that resolution was effected but racemization occurred during the removal of the bromocamphorsulfonic acid. The iodide itself also racemized quickly. Kamai ⁶⁴ resolved the arsonium iodide shown in Fig. 123 by means of the *d*-bromocamphorsulfonate. After crystallization of

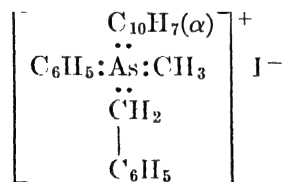


Fig. 122

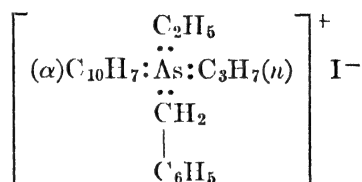


Fig. 123

this salt, it was treated with potassium iodide. The active iodide with $[\alpha]_D^{25}$ of $+9.8^\circ$ in acetone was obtained, but rapidly racemized.

A much more satisfactory example of an optically active arsenic atom was found in *p*-carboxyphenylmethylethylarsine sulfide (Fig. 124),

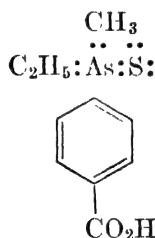


Fig. 124

which was resolved by Mills and Raper ⁶⁵ in 1925. The constitution of this compound is similar to the amine and phosphine oxides, but whereas the latter are basic and form salts, the tertiary arsine sulfides are neutral and the compound was resolved by salt formation of the carboxyl group with brucine. Both *d*- and *l*-forms were obtained, $[\alpha]_D = \pm 19^\circ$. It seems that one of the factors contributing to the success of the resolution is the fact that the arsenic atom was left undisturbed by the processes of salt formation and decomposition necessary to the resolution.

Chatt and Mann ⁶⁶ have prepared ethylene- α,β -bis-(phenyl-*n*-butyl-

⁶⁴ Kamai, *Ber.*, **66**, 1779 (1933).

⁶⁵ Mills and Raper, *J. Chem. Soc.*, **127**, 2479 (1925).

⁶⁶ Chatt and Mann, *ibid.*, 610, 1622 (1939).

arsine) which has been converted into the *bis*-(methopicate) (Fig. 125). This latter compound was separated into two isomers which represent *meso* and racemic forms. Two similar 4-covalent arsenic atoms make this isomerism possible.

The same diarsine was also converted to the *bis*-(arsine sulfide) (Fig. 126) which was isolated in *meso* and racemic modifications. One was rapidly converted to the other by heating. On the other hand the diarsine coordinated with palladous chloride gave two diastereoisomeric non-ionic compounds (Fig. 127) which were extremely stable and did not

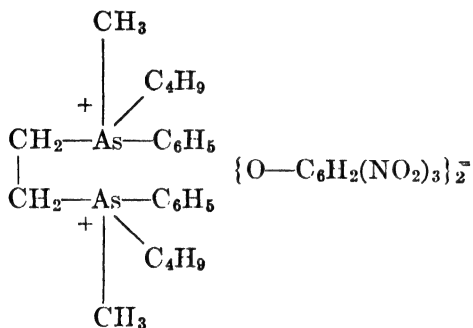


FIG. 125

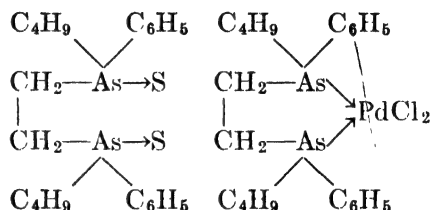


FIG. 126

FIG. 127

undergo interconversion even in molten state. This stability may be due to the fact that the asymmetric arsenic atoms in the palladium compound form part of a chelated ring and thus cannot readily undergo a change of configuration.

There is considerable evidence from spectroscopic and electron diffraction studies to show that stereochemically the 3-covalent arsenic atom can be regarded as being at the top apex of a partially flattened tetrahedron,⁶⁷ the intervalency angles at the arsenic atom being about 100° instead of the normal value (60°).

Organic compounds containing 3-covalent arsenic have now been prepared, and the results are confirmatory of the physical data on the structure of the arsenic atom. Allen, Wells, and Wilson⁶⁸ treated 7-chloro-7,12-dihydro- γ -benzophenarsazine (Fig. 128) with silver *d*-bromocamphorsulfonate and obtained two diastereoisomeric compounds, Fig. 121, with M_D of +211.4° and +358.4°, respectively. The existence of these two diastereoisomers may be due to the asymmetric arsenic atom since no optical isomers of secondary amines are known, or it may

⁶⁷ Sutherland, Lee, and Wu, *Trans. Faraday Soc.*, **35**, 1373 (1939); Pauling and Brockway, *J. Am. Chem. Soc.*, **57**, 2684 (1935); Gregg, Hampson, Jenkins, Jones, and Sutton, *Trans. Faraday Soc.*, **33**, 852 (1937); Springall and Brockway, *J. Am. Chem. Soc.*, **60**, 996 (1938); Bradley, *Phil. Mag.*, **47**, 657 (1924).

⁶⁸ Allen, Wells, and Wilson, *J. Am. Chem. Soc.*, **56**, 233 (1934).

be due to molecular asymmetry produced by a folded structure of the molecule.

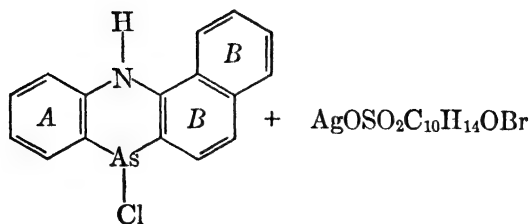


FIG. 128

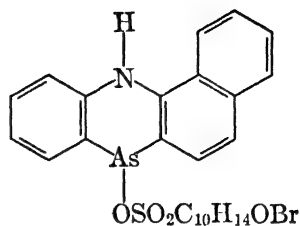


FIG. 129

Lesslie and Turner⁶⁹ prepared 10-methylphenoxarsine-2-carboxylic acid shown in Fig. 130.

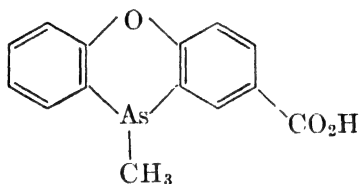


FIG. 130

dl-Compound; m. p. 202–203°

d-Isomer; m. p. 135–136°, $[\alpha]_{D}^{25} + 95^\circ$

l-Isomer, m. p. 135–136°, $[\alpha]_{D}^{25} - 96^\circ$

The acid was resolved by means of strychnine, the two optical antipodes were obtained with the rotations indicated. The authors suggested that the asymmetry of the molecule is not due to the arsenic atom alone, but that the molecule possesses a folded structure about the oxygen-arsenic axis, Fig. 131. The non-planar position of the rings seems reasonable in view of the measurements of the angle between the valencies of the oxygen atom. The two optical isomers may be represented by the figures shown in Fig. 131. The addition of methyl or ethyl iodide to the

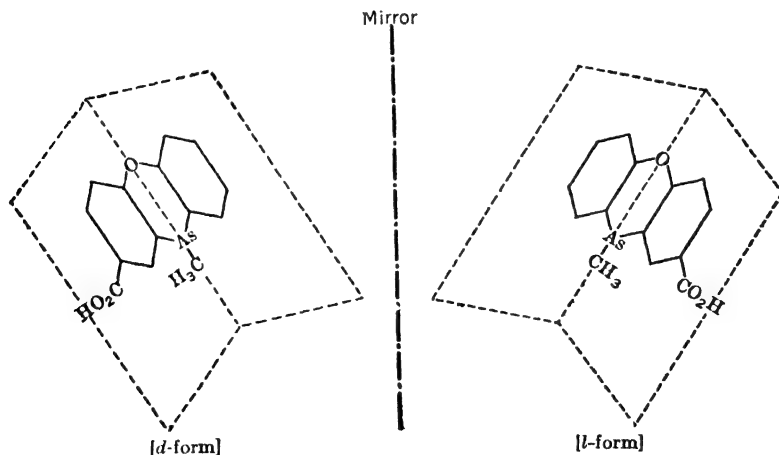


FIG. 131

⁶⁹ Lesslie and Turner, *J. Chem. Soc.*, 1170 (1934).

optically active forms caused racemization to occur. If the optical activity is due to an asymmetric arsenic atom, the dimethylarsonium compound should be inactive. The addition compound with ethyl iodide (Fig. 132) should still contain an asymmetric arsenic atom as the

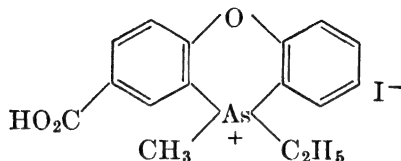


FIG. 132

arsonium ion and should retain its asymmetry. It was suggested that the racemization taking place when the active compound is treated with an alkyl halide is due to the fact that the conversion of the trivalent arsine to the arsonium salt involves a diminution in the effective size of the arsenic atom. The ionic radius of the arsenic in the arsonium ion is smaller than that of the arsenic in an arsine. According to Lesslie and Turner this change in the size of the arsenic atom would cause such agitation in the folded structure that racemization would result.

The compounds corresponding to Fig. 130 with a phenyl or ethyl group in place of methyl on the arsenic atom were also resolved.⁷⁰ Oxidation of the active form of the phenyl derivative resulted in complete loss of activity. On the other hand, it was possible to resolve 10-phenylphenoxarsine-10-oxide-2-carboxylic acid⁷¹ (Fig. 133). The active forms

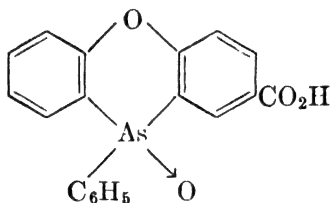


FIG. 133

were relatively unstable. Owing to the similarity in size between the positively charged arsenic and oxygen atoms, the stability of a folded configuration in this molecule might be so decreased that optical activity dependent on it would not occur. This molecule, therefore, probably represents molecular dissymmetry of an arsenic oxide which previously all attempts have failed to demonstrate.⁷²

⁷⁰ Lesslie and Turner, *ibid.*, 1051, 1268 (1935); 730 (1936).

⁷¹ Lesslie, *ibid.*, 1050 (1939).

⁷² Burrows and Turner, *ibid.*, **119**, 426 (1921); Aeschlimann and McClelland, *ibid.* **125**, 2025 (1924); Aeschlimann, *ibid.*, **127**, 811 (1925).

Chatt and Mann ⁷³ point out that the previous work on the phenoxarsine derivatives can be interpreted on the assumption either that the three rings are coplanar and the R group on the arsenic atom projects above or below this plane or that the intervalency angle C—As—C within the ring has a value which necessitates a folding of the molecule about the O—As axis. In the latter case, a planar distribution of the valencies of the arsenic atom, though unlikely, is not excluded. These investigators have prepared and studied 5,10-di-*p*-tolyl-5,10-dihydroarsanthrene (Fig. 134), which has resulted in more decisive evidence for

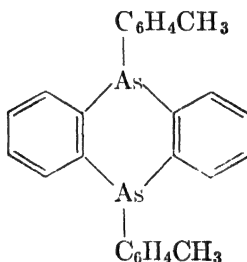


FIG. 134

the non-planar valency disposition of the 3-covalent arsenic atom in its organic compounds. Assuming that the valencies of each arsenic atom are to be mutually inclined at an angle of about 100° , the molecule cannot be planar. The folding can apparently lead to the production of three isomeric forms shown in Figs. 135, 136, and 137.

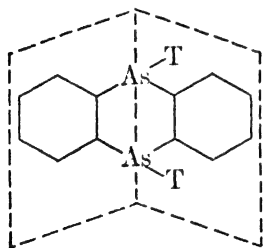


FIG. 135

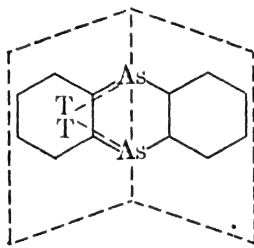


FIG. 136

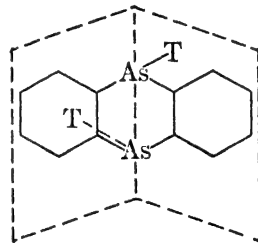


FIG. 137

Upon construction of the models, it becomes evident at once that, owing to the small angle, the two *cis*-tolyl groups (denoted by the letter T) in Fig. 136 become almost coincident in space and that this form cannot therefore exist. Satisfactory models of Figs. 135 and 137 can be readily constructed. The experimental results led to the isolation of two stable forms, conforming presumably to Figs. 135 and 137. The two

⁷³ Chatt and Mann, *ibid.*, 1184 (1940).

isomers by the action of bromine gave the same tetrabromide, 5,10-ditolyl-5,10-dihydroarsanthrene 5,5,10,10-tetrabromide (Fig. 138) which in turn was hydrolyzed to a single tetrahydroxide.

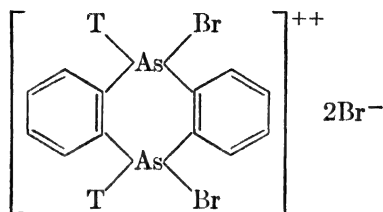


FIG. 138

Boron, Beryllium, Copper, and Zinc. These four elements, constituting the other known elements of the tetrahedral group, are discussed together because the tetrahedral character of each has been demonstrated by the formation of spiranes. These spiranes have the tetrahedral element as the spiro-atom, and the two rings are formed as the result of chelation.

Boric acid reacts with two molecules of salicylic acid to produce the complex shown by Fig. 140.

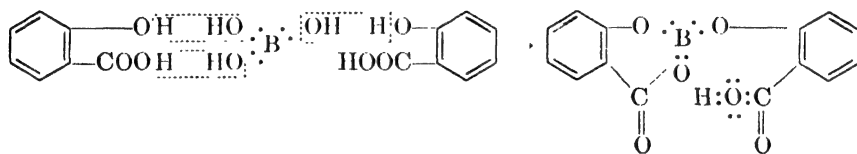


FIG. 139

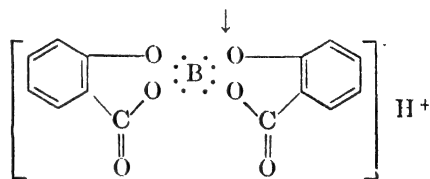


FIG. 140

Boron compounds normally have six electrons in the valence shell of the boron atom (Fig. 139), but, by sharing an additional pair from the oxygen of the carboxyl group (Fig. 139) left after ionization of the hydrogen atom, it is able to form the more stable octet and thus becomes a spiro-atom in the chelate (p. 1868) compound (Fig. 140). Böeseken⁷⁴ fractionally crystallized the strychnine salts of this complex compound and obtained a dextrorotatory fraction with $[\alpha]_D = +22.6^\circ$. The other

⁷⁴ Böeseken and Meulenhoff, *Proc. Acad. Sci. Amsterdam*, **27**, 174 (1924); Rosenheim and Vermehren, *Ber.*, **57**, 1337 (1924).

fraction was levorotatory. The optical activity of this boron complex not only establishes the chelate structure, but also shows that the distribution of the valence forces about the boron must be tetrahedral. It should be noted that the model of this complex, using a planar boron atom, would possess a plane of symmetry and hence be non-resolvable. Either a planar or pyramidal structure would predict geometrical isomers which have not been found.

Beryllium is normally bivalent, containing four electrons in the valence shell of most of its compounds. However, the reaction of beryllium carbonate with the brucine salt of the enolic form of benzoyl-pyruvic acid produces the complex shown in Fig. 141, in which the

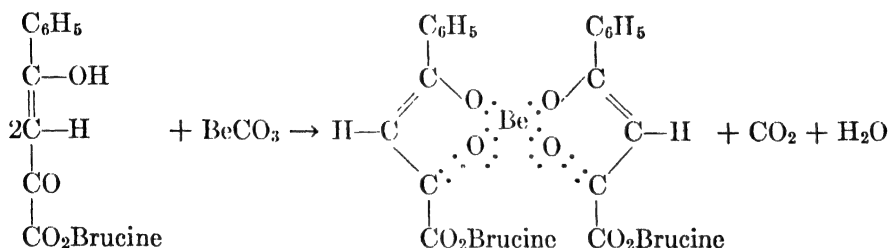


FIG. 141

beryllium has shared an additional four electrons in order to complete its octet and form the chelate compound with the beryllium atom as the spiro-atom of the spirane.

Mills and Gotts⁷⁵ fractionally crystallized these brucine salts and obtained two diastereoisomeric salts which showed mutarotation in chloroform to the same value.

- $$\left. \begin{array}{l} 1. \text{ Fraction } [\alpha]_{5461} = +25.0^\circ \\ 2. \text{ Fraction } [\alpha]_{5461} = -11.8^\circ \end{array} \right\} \xrightarrow{\text{Mutarotation}} [\alpha] = +5.0^\circ$$

Decomposition of the salts by dimethylamine gave values of $+1.1^\circ$ and -0.6° for the two forms of the beryllium complex. The two forms racemized very quickly. Copper and zinc formed chelate compounds of the same type as shown for beryllium when copper acetate or zinc carbonate was substituted for beryllium carbonate in the initial reaction. Fractionation of their brucine salts also produced mutarotating diastereoisomeric forms.

Palladium. Reihlen and Hühn⁷⁶ crystallized the *d*-bromocamphor-sulfonate of the complex palladium ion shown in Fig. 142 and obtained

⁷⁵ Mills and Gotts, *J. Chem. Soc.*, 3121 (1926).

⁷⁶ Reihlen and Hühn, *Ann.*, **489**, 42 (1931).

two diastereoisomeric salts. One salt had a molecular rotation of $+582^\circ$ with M_D for the *dextro* palladium complex ion of $+36^\circ$. The other salt

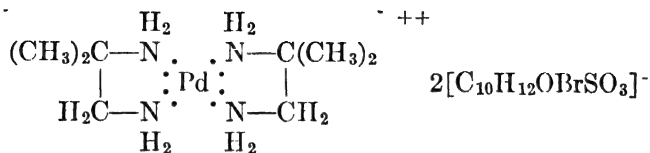


FIG. 142

had M_D of $+506^\circ$, which indicates a molecular rotation of -40° for the *levo* palladium complex ion.

Platinum. Reihlen and Hühn ⁷⁶ also obtained evidence indicating asymmetry of the platinum complexes shown in Fig. 143 and Fig. 144 by crystallization of their *d*-bromocamphorsulfonates.

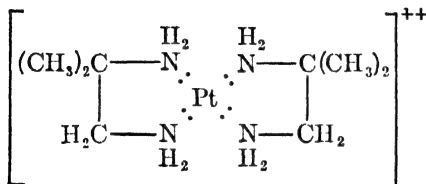


FIG. 143

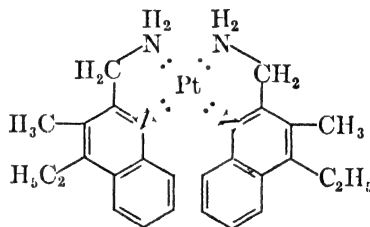


FIG. 144

Elements with an Octahedral Distribution of Valencies

The classical investigations of Werner, Pfeiffer, Jaeger, and others on the structure of various coördination complex salts have established the fact that certain of these may exhibit optical isomerism, and that the probable distribution of the valencies of all types is octahedral about the central atom. These compounds and their isomerism have been thoroughly treated in inorganic textbooks and books on stereochemistry; hence only the fundamental ideas concerned will be discussed in this section. It is important to note that the same principles already cited in respect to carbon again apply here. For optical isomerism the prerequisite is an asymmetric molecule.

The general structural types which have been resolved into optical enantiomorphs are as follows:

I. Type MA_3 . (M = metal, A = a bivalent coördinating group.)

The central atom has its six valencies distributed and used by the groups A in such a manner that non-superimposable mirror images

result (Figs. 1 and 2). It is customary to represent the spatial formulas by the figures shown rather than by means of an octahedron, but by joining the six points about the central atom, an octahedron results (Fig. 3).

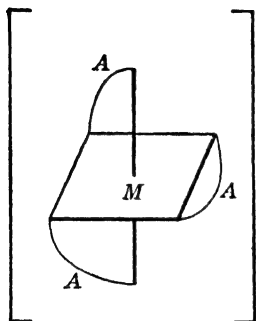


FIG. 1

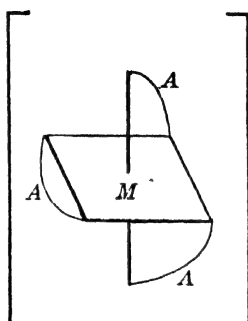


FIG. 2

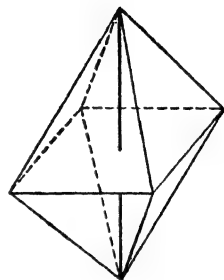


FIG. 3

Specific examples of compounds of this type are shown in Table I.

II. Type MA_2a_2 and MA_2B . (A and B = different bivalent coordinating groups; a = monovalent coordinating groups.)

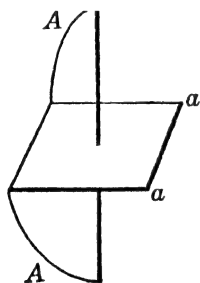


FIG. 4

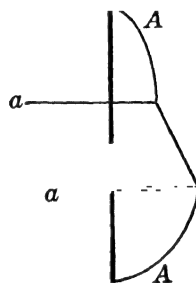


FIG. 5

The mirror-image relationships of this type are shown in Figs. 4 and 5, and Figs. 6 and 7.

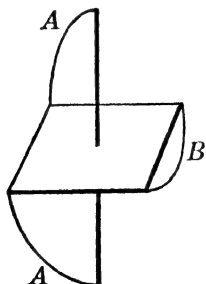


FIG. 6

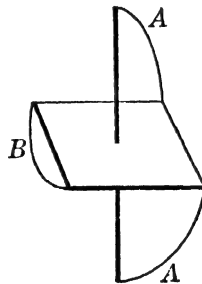


FIG. 7

TABLE I
OPTICALLY ACTIVE COMPLEX IONS OF THE TYPE MA_3

| <i>Anions</i> | |
|--|---|
| $\left[\text{Al} \left(\begin{array}{c} \diagup \text{O}-\text{C}=\text{O} \\ \diagdown \text{O}-\text{C}=\text{O} \end{array} \right)_3 \right]^-$ | $\left[\text{Ir} \left(\begin{array}{c} \diagup \text{O}-\text{C}=\text{O} \\ \diagdown \text{O}-\text{C}=\text{O} \end{array} \right)_3 \right]^-$ |
| $\left[\text{As} \left(\begin{array}{c} \diagup \text{O}-\text{C}_6\text{H}_4 \\ \diagdown \text{O}-\text{C}_6\text{H}_4 \end{array} \right)_3 \right]^-$ | $\left[\text{Ir} \left(\begin{array}{c} \diagup \text{O}-\text{C}=\text{O} \\ \diagdown \text{O}-\text{C}=\text{O} \\ \text{CH}_2 \end{array} \right)_3 \right]^-$ |
| $\left[\text{Co} \left(\begin{array}{c} \diagup \text{O}-\text{C}=\text{O} \\ \diagdown \text{O}-\text{C}=\text{O} \end{array} \right)_3 \right]^-$ | $\left[\text{Rh} \left(\begin{array}{c} \diagup \text{O}-\text{C}=\text{O} \\ \diagdown \text{O}-\text{C}=\text{O} \end{array} \right)_3 \right]^-$ |
| $\left[\text{Cr} \left(\begin{array}{c} \diagup \text{O}-\text{C}=\text{O} \\ \diagdown \text{O}-\text{C}=\text{O} \end{array} \right)_3 \right]^-$ | $\left[\text{Rh} \left(\begin{array}{c} \diagup \text{O}-\text{C}=\text{O} \\ \diagdown \text{O}-\text{C}=\text{O} \\ \text{CH}_2 \end{array} \right)_3 \right]^-$ |
| $\left[\text{Cr} \left(\begin{array}{c} \diagup \text{O}-\text{C}=\text{O} \\ \diagdown \text{O}-\text{C}=\text{O} \\ \text{CH}_2 \end{array} \right)_3 \right]^-$ | $\left[\text{Pt} \left(\begin{array}{c} \diagup \text{O}-\text{C}=\text{O} \\ \diagdown \text{O}-\text{C}=\text{O} \end{array} \right)_3 \right]^-$ |
| $\left[\text{Fe} \left(\begin{array}{c} \diagup \text{O}-\text{C}=\text{O} \\ \diagdown \text{O}-\text{C}=\text{O} \end{array} \right)_3 \right]^-$ | $\left[\text{Pt} \left(\begin{array}{c} \diagup \text{O}-\text{C}=\text{O} \\ \diagdown \text{O}-\text{C}=\text{O} \\ \text{CH}_2 \end{array} \right)_3 \right]^-$ |
| <i>Cations</i> | |
| $\left[\text{Co} \left(\begin{array}{c} \text{H}_2\text{N}-\text{CH}_2 \\ \\ \text{H}_2\text{N}-\text{CH}_2 \end{array} \right)_3 \right]^{++}$ | $\left[\text{Fe} \left(\begin{array}{c} \text{N} \text{---} \text{C}_6\text{H}_4 \\ \\ \text{N} \text{---} \text{C}_6\text{H}_4 \end{array} \right)_3 \right]^{++}$ |
| $\left[\text{Co} \left(\begin{array}{c} \text{H}_2\text{N}-\text{CH}_2 \\ \\ \text{H}_2\text{N}-\text{CH}_2 \\ \text{CH}_2 \end{array} \right)_3 \right]^{++}$ | $\left[\text{Ir} \left(\begin{array}{c} \text{H}_2\text{N}-\text{CH}_2 \\ \\ \text{H}_2\text{N}-\text{CH}_2 \end{array} \right)_3 \right]^{++}$ |
| $\left[\text{Co} \left(\begin{array}{c} \text{H}_2\text{N}-\text{CH}_2 \\ \\ \text{H}_2\text{N}-\text{CH}_2 \end{array} \right)_3 \right]^{++}$ | $\left[\text{Rh} \left(\begin{array}{c} \text{H}_2\text{N}-\text{CH}_2 \\ \\ \text{H}_2\text{N}-\text{CH}_2 \end{array} \right)_3 \right]^{++}$ |
| $\left[\text{Co} \left(\begin{array}{c} \text{H}_2\text{N}-\text{CH}_2 \\ \\ \text{H}_2\text{N}-\text{CH}_2 \end{array} \right)_3 \right]^{++}$ | $\left[\text{Pt} \left(\begin{array}{c} \text{H}_2\text{N}-\text{CH}_2 \\ \\ \text{H}_2\text{N}-\text{CH}_2 \end{array} \right)_3 \right]^{++}$ |
| $\left[\text{Cr} \left(\begin{array}{c} \text{H}_2\text{N}-\text{CH}_2 \\ \\ \text{H}_2\text{N}-\text{CH}_2 \end{array} \right)_3 \right]^{++}$ | $\left[\text{Pt} \left(\begin{array}{c} \text{CH}_3 \\ \\ \text{H}_2\text{N}-\text{CH} \\ \\ \text{H}_2\text{N}-\text{CH}_2 \end{array} \right)_3 \right]^{++}$ |
| $\left[\text{Zn} \left(\begin{array}{c} \text{H}_2\text{N}-\text{CH}_2 \\ \\ \text{H}_2\text{N}-\text{CH}_2 \end{array} \right)_3 \right]^{++}$ | <i>Neutral Compound</i> |
| | $\text{Co} \left(\begin{array}{c} \text{O}-\text{C}=\text{O} \\ \\ \text{H}_2\text{N}-\text{CH} \\ \\ \text{CH}_3 \end{array} \right)_3$ |

Specific examples of compounds of the second type are shown in Tables II and III.

TABLE II
OPTICALLY ACTIVE COMPLEX IONS OF THE TYPE MA_2a_2

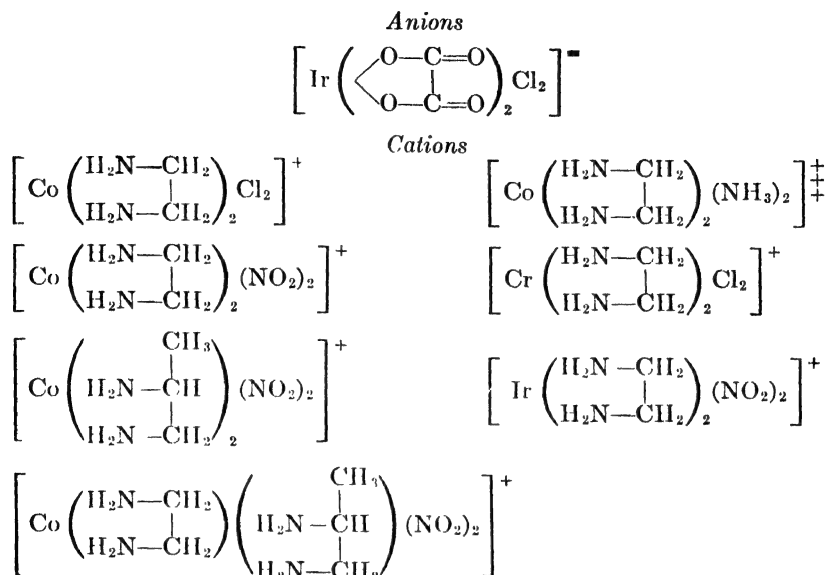
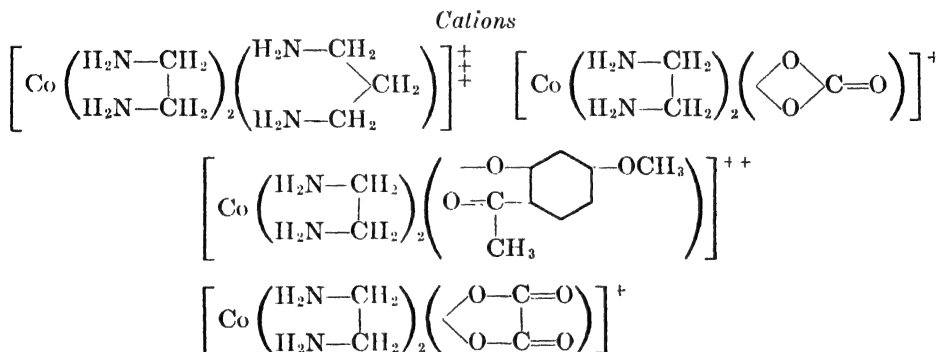
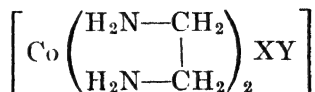


TABLE III
OPTICALLY ACTIVE COMPLEX IONS OF THE TYPE MA_2B



III. Type MA_2ab . (A = bivalent coördinating group; a and b = different monovalent coördinating groups.)

Many compounds corresponding to Figs. 8 and 9 which represent the mirror-image relationships are known for complexes of cobalt. The cation has the general formula



where X and Y are various combinations of Cl, Br, NO₂, NCS, H₂O, NH₃, NH₂OH. An anion of this type is:

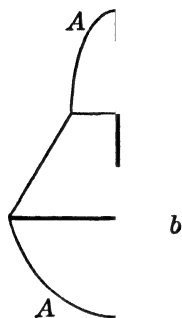
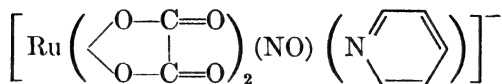


FIG. 8

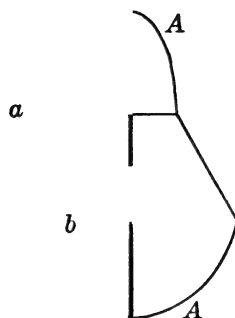


FIG. 9

IV. Type MA₂b₂.

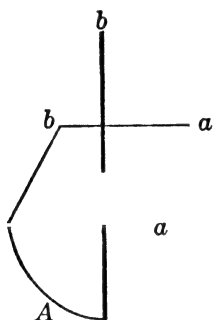


FIG. 10

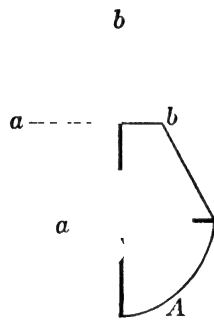
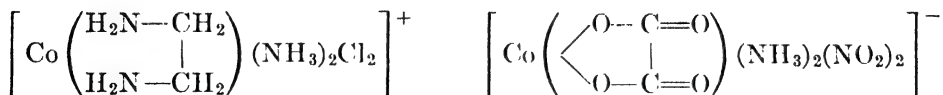


FIG. 11

The compounds corresponding to the Figs. 10 and 11 which have been resolved are:



Elements with a Planar Distribution of Valencies

The chief compounds in which there is experimental evidence for a planar arrangement of groups are the 4-covalent compounds of bivalent palladium, platinum, and nickel. These same elements also possess an octahedral configuration in their 6-covalent compounds. Comparison

of the octahedral model, Fig. 1, with the planar arrangement of Fig. 2 in which the metal (M) occupies the center of a square with the four groups at the corners shows that this may be regarded as a special case of elements with octahedral configuration in which the two *b* groups are missing. It is well known that compounds with 4-covalent groups at-

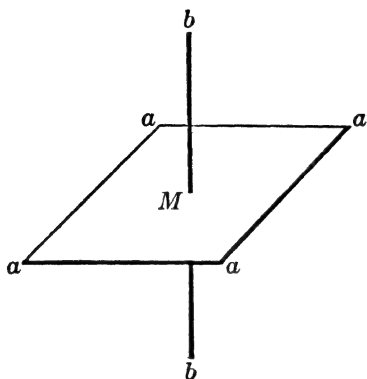


FIG. 1

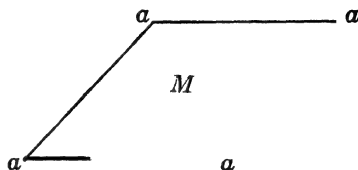


FIG. 2

tached to the metal may be converted to compounds with 6-covalent groups.

Werner, as early as 1893, proposed a planar configuration for 4-covalent compounds of platinum and palladium which predicted *cis* and *trans* isomerides of the types shown in Figs. 3 and 4. Definite proof

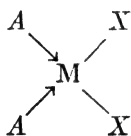


FIG. 3

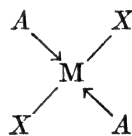


FIG. 4

of the planar configuration and existence of such isomers has been difficult to obtain owing to the difficulties involved in determining the exact molecular structure and molecular weight. For example, a pink and a yellow form of $(\text{NH}_3)_2\text{PdCl}_2$ were known for a long time and the isomerism was explained on a *cis-trans* basis. However, it was proved later that the yellow form is monomolecular, whereas the pink modification is bimolecular⁷⁷ and has the structure $[\text{Pd}(\text{NH}_3)_4][\text{PdCl}_4]$. Numerous other examples of supposed *cis-trans* isomers have been reported, some of which appear to be authentic.

In 1922, it was noted⁷⁸ that $\text{K}_2[\text{PdCl}_4]$, $(\text{NH}_4)_2[\text{PdCl}_4]$, and

⁷⁷ Drew, Pinkard, Preston, and Wardlaw, *J. Chem. Soc.*, 1895 (1932).

⁷⁸ Dickinson, *J. Am. Chem. Soc.*, **44**, 2404 (1922); Lowry, *J. Soc. Chem. Ind.*, **42**, 316 (1923).

$K_2[PtCl_4]$ formed tetragonal crystals, and x-ray analysis indicated that the metal was at the center of a square with the four chlorine atoms at the corners. From considerations of wave mechanics, Pauling ⁷⁹ in 1931 deduced a probable planar distribution of the groups in 4-covalent compounds of platinum, palladium, and nickel. The electronic formation of such planar compounds should result in a definite decrease of the paramagnetic moment, and for nickel this should become zero.

Nickel. Confirmation of this prediction was obtained by Sugden,⁸⁰ who isolated two *cis-trans* isomers of nickel *bis*-benzylmethylglyoxime to which the planar structures shown in Figs. 5 and 6 were

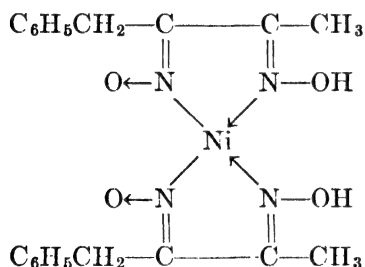


FIG. 5

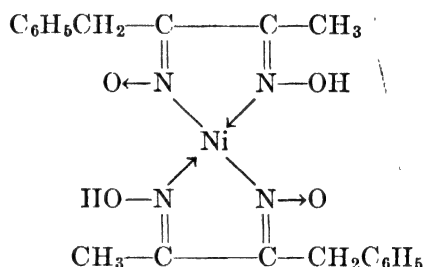


FIG. 6

assigned. These two forms were found to be diamagnetic, whereas a tetrahedral configuration about the 4-covalent nickel (a spiro-atom) should lead to paramagnetic optical enantiomorphs.

Palladium. Dwyer and Mellor ⁸¹ also obtained two forms of palladium *bis*-benzylmethylglyoxime, analogous to the above nickel isomerides, and found that they were non-resolvable. Pinkard, Sharratt, and Wardlaw ⁸² prepared the two isomerides shown in Figs. 7 and 8 and showed that they were monomeric.

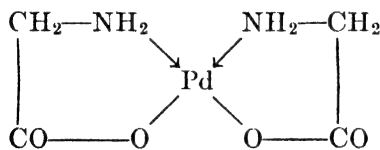


FIG. 7

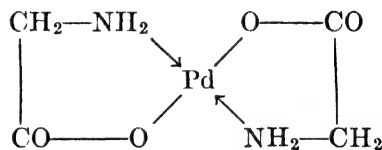


FIG. 8

Grinberg and Schulman ⁸³ reported the isolation of two isomerides of each of the compounds $(NH_3)_2PdCl_2$ and $(\text{pyridine})_2PdCl_2$.

⁷⁹ Pauling, *J. Am. Chem. Soc.*, **53**, 1367 (1931).

⁸⁰ Sugden, *J. Chem. Soc.*, 246 (1932).

⁸¹ Dwyer and Mellor, *J. Am. Chem. Soc.*, **56**, 1551 (1934).

⁸² Pinkard, Sharratt, and Wardlaw, *J. Chem. Soc.*, 1012 (1934).

⁸³ Grinberg and Schulman, *Compt. rend. acad. sci., U.R.S.S.*, **1**, 218 (1933).

Lidstone and Mills ⁸⁴ have resolved the complex palladous salt shown in Fig. 9 by means of *d*- and *l*-diacetyltartaric acids. This molecule

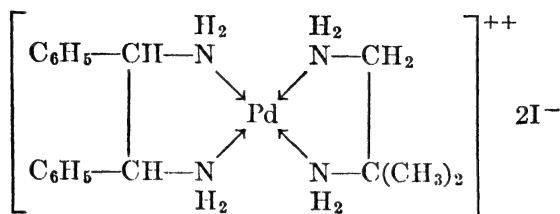


FIG. 9

would possess a plane of symmetry if the palladium atom had a tetrahedral arrangement of the coördinated groups but is asymmetric if the four valencies attached to the palladium atom are planar. It was shown that the stilbene diamine portion retained its *meso* configuration in the complex salt and hence the resolution is due to the molecular dissymmetry of the complex.

Platinum. Numerous examples of *cis-trans* isomers of 4-covalent platinum compounds have been described. Hantzsch ⁸⁵ obtained two forms of the compound shown in Fig. 10, and Schenck and Hengler ⁸⁶ obtained the quinoline analogs, Fig. 11. The two isomeric compounds

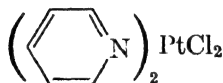


FIG. 10

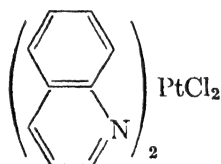


FIG. 11

of Figs. 12 and 13 were found to differ chemically and also in their x-ray diffraction patterns.⁸⁷ Two isomeric forms of the platino-glycine com-

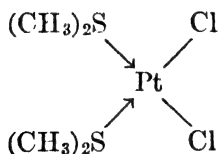


FIG. 12

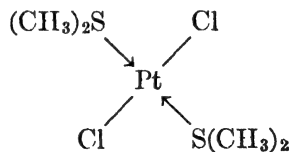


FIG. 13

⁸⁴ Lidstone and Mills, *J. Chem. Soc.*, 1754 (1939).

⁸⁵ Hantzsch, *Ber.*, **59**, 2761 (1926).

⁸⁶ Schenck and Hengler, *Arch. Eisenhüttenw.*, **5**, 209 (1931-1932).

⁸⁷ Angell, Drew, and Wardlaw, *J. Chem. Soc.*, 349 (1930); Cox, Saenger, and Wardlaw *ibid.*, 182 (1934).

plex, Fig. 14, analogous to the palladium complex have been obtained.⁸⁸

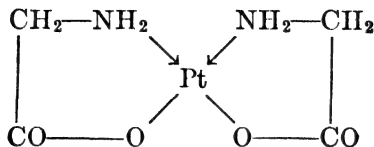


FIG. 14

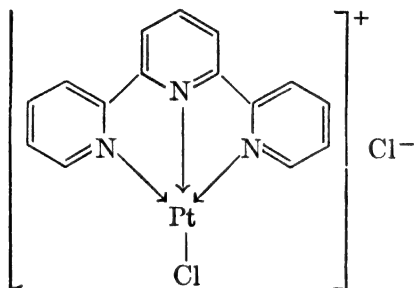


FIG. 15

A red and a black form of the *tris*-pyridino complex, Fig. 15, have been obtained by Morgan and Burstall.⁸⁹ This complex is very interesting because the construction of the model of this molecule shows that the three pyridine rings are in the same plane. It may also be noted from the model that chelation can occur without undue strain only if the double bonds in at least two of the pyridine rings occupy fixed positions (i.e., do not oscillate or resonate between the two Kekulé structures). If either of the two forms obtained is monomolecular, it indicates a planar distribution of the valence forces about the platinum atom.

An unique proof of a planar distribution of the valencies about 4-covalent platinum has been obtained recently by Mills and Quibell,⁹⁰ who prepared *meso*-stilbenediamino-isobutylenediamino platinous salts with the structure shown in Fig. 16.

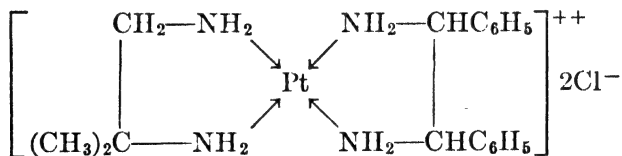


FIG. 16

⁸⁸ Grinberg and Ptitzuin, *J. prakt. Chem.*, **136**, 143 (1933); Pinkard, Sharratt and Wardlaw, *J. Chem. Soc.*, 1012 (1934).

⁸⁹ Morgan and Burstall, *ibid.*, 1498 (1934).

⁹⁰ Mills and Quibell, *ibid.*, 839 (1935).

Examination of the model of this compound using a planar platinum atom reveals the fact that such a model does not possess a plane of symmetry (Fig. 17), and hence should be resolvable.

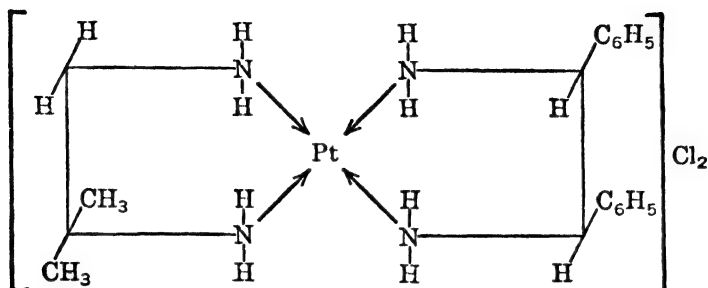


FIG. 17

If, however, the platinum atom is tetrahedral (similar to the spiranes) then the molecule possesses a plane of symmetry, and the molecule should be non-resolvable. Examination of Fig. 18 shows that the plane *PPPP* divides the molecule into halves which are mirror images.

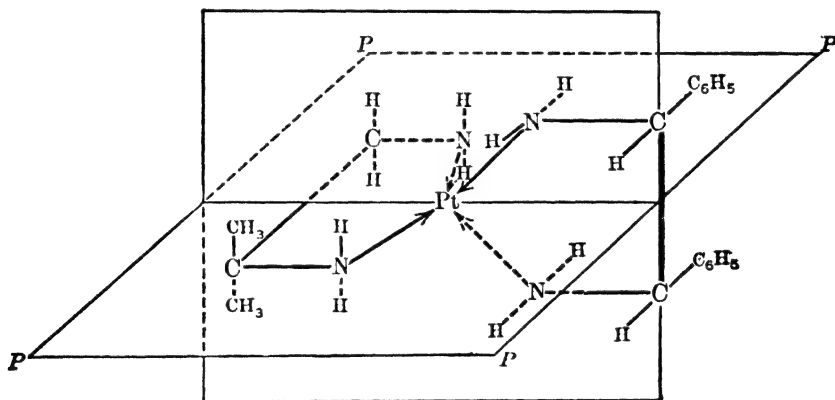


FIG. 18

Experimentally it was established that the molecule was resolvable into *d*- and *l*-forms, $[\alpha]_{5461} = \pm 48.5^\circ$. Cryoscopic examination of the salt showed that it resembled barium chloride in its behavior, and thus indicates the existence of only three ions. Decomposition by alkalis gave the optically inactive diamines and thus demonstrated that no inversion and resolution of the *meso*-diaminostilbene portion took place. The results constitute most unusual evidence in favor of a planar configuration for 4-covalent platinum. It is true that an irregular tetrahedral arrangement or pyramidal arrangement would also predict resolution of the molecule, but there is no evidence for such assumptions.

PART XI. *cis-trans* ISOMERISM (GEOMETRIC ISOMERISM)

C. S. MARVEL

Introduction

A second type of stereoisomerism has been observed in organic molecules that contain two unsymmetrically substituted atoms attached to each other by a double union, in certain cyclic structures, and in a few terphenyl derivatives where *ortho* substitution introduces steric hindrance at the points of union between the phenyl groups. This type of isomerism is usually explained on the basis of restricted rotation in the molecule in question, and all the observed cases can be correlated by means of this theory.

In an open-chain molecule, free rotation about a single covalent bond is assumed to be possible. The number of isomers of such compounds is generally in agreement with this hypothesis. However, if there are two points of attachment between adjacent atoms, as when a double covalent bond is present in a molecule, free rotation is apparently no longer possible. With proper substitution around the atoms which are doubly bound to each other, isomerism due to different geometric arrangements of the groups in space becomes possible. This type of isomerism is called *cis-trans* or geometrical isomerism.

cis-trans Isomerism in cyclic molecules can be attributed to restricted rotation due to the ring structure. The size of the ring and the nature of the substituents have an important effect on the freedom of rotation around the single bonds in the ring, and a complete discussion of these factors will be reserved until later. Recently *cis-trans* isomerism has been observed in certain *p*-terphenyl derivatives which are substituted in the positions *ortho* to the unions between the phenyl groups. In these compounds the theory of restricted rotation around the bonds between the phenyl groups serves to correlate these examples of *cis-trans* isomerism with the classes previously mentioned.

The various types of *cis-trans* isomers may for convenience be classified as follows:

1. Compounds containing double bonds.
 - (a) Carbon to carbon; olefins.
 - (b) Carbon to nitrogen; oximes, hydrazones, osazones, semi-carbazones, etc.
 - (c) Nitrogen to nitrogen; diazo compounds, azo compounds, azoxy compounds, etc.

2. Cyclic compounds.
 - (a) Carbocyclic.
 - (b) Heterocyclic.
 - (c) Condensed ring systems.
3. Sterically hindered single bond compounds of the terphenyl type.

This system of classification is used in the following discussion.

Compounds Containing Double Bonds

Since carbon and nitrogen atoms are known to have a tetrahedral structure, a double bond involving these atoms may be pictured (Fig. 1) by two tetrahedrons sharing one edge in common. Thus, the double bond should be a fairly rigid structure around which no rotation can occur. The single bond may be best illustrated by a diagram (Fig. 2) showing two tetrahedrons having one apex in common. Free rotation around this common point would be expected.

In a molecule of the type first shown (Fig. 1), if each atom is attached to two different groups, *a* and *b*, two space formulas for the molecules can be constructed (Figs. 3 and 4). In one of these formulas it may be seen

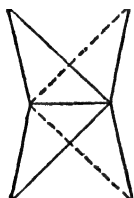


FIG. 1

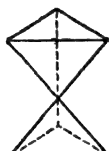


FIG. 2

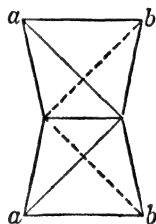


FIG. 3

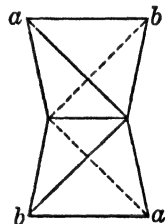
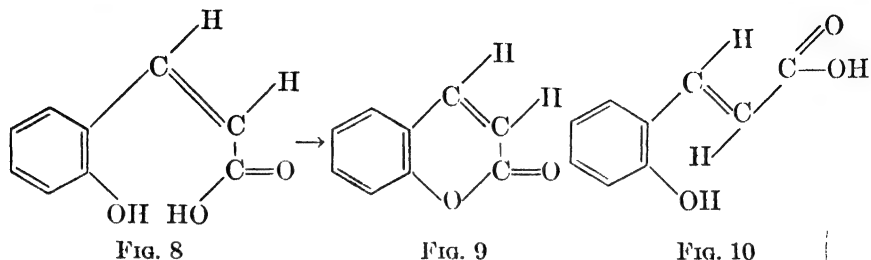


FIG. 4

that the two *a* groups are closer together than they are in the other (Fig. 4). If a plane is passed through that edge of the tetrahedrons which is shared between them and continued in each direction so as to bisect the lines joining the *a* and *b* groups, the like groups are either on the same side of this plane, that is, in the *cis* positions (Fig. 3), or they fall on opposite sides of this plane and are in the *trans* positions (Fig. 4). The four groups (*a a b b*) fall in one plane; hence the mirror image of each form is identical with the object, and no optical isomers can exist in this series.

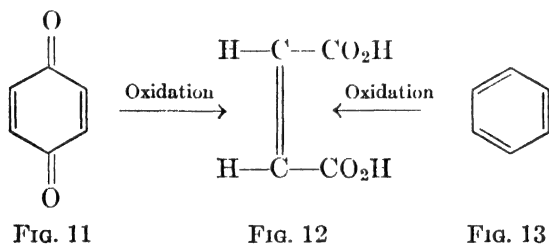
It can also be seen that each of the atoms joined by the double union must be unsymmetrically substituted. When one of the atoms carries two *a* groups, and is thus symmetrical (Figs. 5 and 6), the two molecules are superimposable, and hence do not represent isomers. Only one pair

Likewise, in the case of the *o*-hydroxycinnamic acids, one is converted spontaneously into coumarin (Fig. 9), and is, therefore, the *cis* form (Fig. 8), whereas the other does not form a lactone readily, and consequently is assigned the *trans* configuration (Fig. 10).⁵

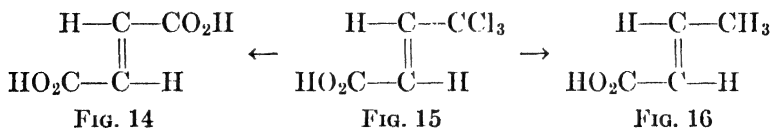


This conversion to a cyclic compound must occur under very carefully regulated conditions if it is to be considered a safe procedure for structural proof. Many reagents cause one isomer to change into the other, and with such reagents, compounds of the *trans* type may also yield cyclic compounds.

It is often possible to prepare the *cis* isomer from a cyclic compound by the opening of the ring. Thus, the oxidation of *p*-benzoquinone (Fig. 11) or of benzene (Fig. 13) leads to maleic acid (Fig. 12), and not fumaric acid.⁶



If the configurations of a pair of *cis-trans* isomers have been thus established, it is often possible to convert other isomers of unknown configuration into those with known structures. For example, trichlorocrotonic acid (Fig. 15) is converted by hydrolysis into fumaric acid (Fig. 14) and by reduction into the solid crotonic acid (Fig. 16) (m. p.



⁵ Fittig and Ebert, *Ann.*, **226**, 347 (1884); Wislicenus "Raumliche Anordnung," p 49; see Miller and Kinkelin, *Ber.*, **22**, 1705 (1889).

⁶ Kekulé, *Ann.*, **223**, 170 (1884).

72°).⁷ Since fumaric acid is known to have a *trans* configuration, these relationships prove that the trichlorocrotonic acid and the solid crotonic acid must be *trans* isomers. Hence, the liquid form of crotonic acid (m. p. 15°) must be the *cis* isomer.

The configurations of the cinnamic acids have, likewise, been established by the following transformations:

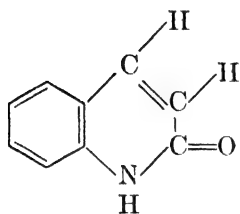


FIG. 17

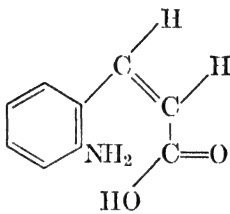


FIG. 18

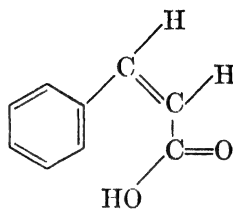


FIG. 19

One of the *o*-aminocinnamic acids readily forms carbostyryl (Fig. 17), and hence possesses the *cis* configuration (Fig. 18). Diazotization and removal of the amino group from this *o*-aminocinnamic acid leads to *cis*-cinnamic acid (Fig. 19).⁸

The establishment of a relationship between a cyclic compound and a *cis* isomer, and the transformation of one of a pair of *cis-trans* isomers into another compound of known configuration, are the only chemical methods of establishing the configuration of isomers in this series. In using these methods for structural work, it is essential to keep in mind that many reagents convert a *cis* to a *trans* isomer or the reverse (see section on interconversion of isomers, p. 453), and hence false relationships may be deduced from superficial experimental work.

Determination of Structure by Study of Physical Properties. A study of various *cis-trans* isomers whose configurations have been established by relating them to cyclic products has shown that there is a surprising regularity in the differences in physical properties between the *cis* forms and the *trans* forms. The *cis* form usually has the lower melting point, the greater solubility in inert solvents, the higher heat of combustion, and, of acids, the higher ionization constant. In Table I are listed the physical properties of a series of isomeric acids showing some of these differences.

Werner pointed out that there is a significant resemblance between the structural formulas of *cis* and *trans* isomers in the olefin series, and *ortho* and *para* isomers in the benzene series.⁹ The unsymmetrical *cis*

⁷ von Auwers and Wissebach, *Ber.*, **56**, 715 (1923).

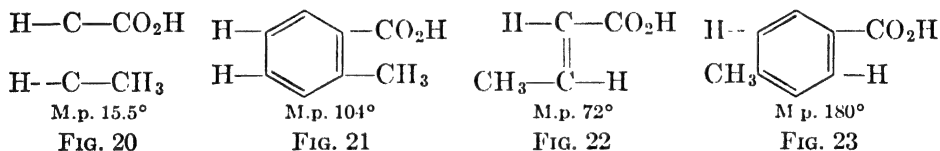
⁸ Stoermer and Heymann, *Ber.*, **45**, 3099 (1912).

⁹ Werner, "Lehrbuch der Stereochemie," Fischer, Jena (1904), p. 212.

TABLE I
SOME PHYSICAL PROPERTIES OF *cis-trans* ISOMERS

| Acid | M. P., °C. | Solubility in Water at 25°, grams per 100 cc. H ₂ O | K_a^{10} | Heat of Combustion, ¹¹ kcal./mole |
|-----------------------------|------------|--|-----------------------|--|
| Maleic..... | 130.0 | 78.8 | 117×10^{-2} | 326.0 |
| Fumaric..... | 286. | 0.7 | 9.3×10^{-2} | 320. |
| <i>cis</i> -Crotonic..... | 15.5 | 40.0 | 3.6×10^{-5} | 486. |
| <i>trans</i> -Crotonic..... | 72. | 8.3 | 2×10^{-5} | 478. |
| <i>cis</i> -Cinnamic..... | 68. | 14.43 | 13.8×10^{-5} | 1047. |
| <i>trans</i> -Cinnamic..... | 133. | 0.1 | 3.5×10^{-5} | 1040. |
| Citraconic..... | 91. | | 34×10^{-2} | 479.1 |
| Mesaconic..... | 202. | | 7.9×10^{-2} | 466.4 |
| Angelica..... | 45. | | 4.9×10^{-5} | 634.8 |
| Tiglic..... | 64. | | 9.4×10^{-6} | 627.4 |

and *ortho* isomers are nearly always lower melting than the corresponding *trans* and *para* isomers. This may be illustrated by comparing *cis*-crotonic acid (Fig. 20), *ortho*-toluic acid (Fig. 21), *trans*-crotonic acid (Fig. 22), and *para*-toluic acid (Fig. 23). Maleic and fumaric acids show similar relationships to *ortho*- and *para*-phthalic acids.



The dissociation constants of the acids in the *cis* and *ortho* series are likewise higher than those in the *trans* and *para* series.¹²

This comparison of the physical properties of olefins and aromatic derivatives has furnished a method for the determination of configuration where all four groups on the carbon atoms joined by the double bond are different. For example, von Auwers compared the chlorocrotonic esters (Figs. 24 and 25) with the chlorotoluic esters (Figs. 26

¹⁰ Ostwald, *Z. physik. Chem.*, **3**, 242, 278, 380 (1889); *Ber.*, **24**, 1106 (1891); Bader, *Z. physik. Chem.*, **6**, 315 (1890); Walden, *ibid.*, **8**, 495 (1891); Kortright, *Am. Chem. J.*, **18**, 370 (1896).

¹¹ Stohmann, *Z. physik. Chem.*, **10**, 416 (1892); Longuinine, *Ann. chim.*, [6] **23**, 189 (1891); Roth, *Ber.*, **46**, 260, 317 (1913).

¹² Langseth, *Z. physik. Chem.*, **118**, 49 (1925).

and 27) and assigned configurations to the olefinic compounds on this basis.¹³

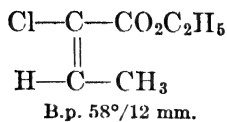


FIG. 24

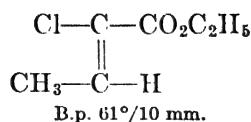


FIG. 25

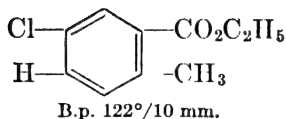


FIG. 26

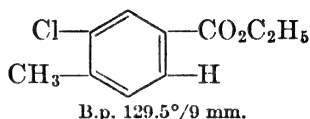


FIG. 27

The assignment of configuration by means of this method of comparison of the physical properties of the isomers with those of the corresponding benzene derivatives must always be tentative because it is known that the relationship between the physical properties in the two series is not absolutely general.¹⁴

Dipole Moments (p. 1752). Recent work on dipole moments has introduced a new physical constant which is useful in assigning definite configuration to relatively simple olefins.¹⁵ From a consideration of the structural formula, the unsymmetrical *cis* form would be expected to have a considerable moment, whereas the more symmetrical *trans* form should have a lower moment. In the halogenated olefins listed in Table II, it may be seen that the dipole-moment measurements give results which are in agreement with the configurations which have been assigned on the basis of the melting points of the isomers.

TABLE II

PHYSICAL PROPERTIES OF DIHALOGENATED ETHYLENES¹⁵

| | M. P. °C. | $\mu \times 10^{18}$ e.s.u. |
|--------------------------------|--------------|--------------------------------|
| <i>cis</i> -Dichloroethylene | -80.5 | 1.89 |
| <i>trans</i> -Dichloroethylene | -50. | 0. |
| <i>cis</i> -Dibromoethylene | -53. | 1.22 |
| <i>trans</i> -Dibromoethylene | -6.5 | 0. |
| <i>cis</i> -Diiodoethylene | -13.8 | 0.76 |
| <i>trans</i> -Diiodoethylene | 72. | 0. |

This method is limited to quite simple molecules of the type

¹³ von Auwers and Harres, *ibid.*, **143**, 1 (1929).

¹⁴ von Auwers and Harres, *ibid.*, **143**, 9 (1929).

¹⁵ Errera, *Compt. rend.*, **182**, 1623 (1926); *Acad. roy. Belg.*, 150 (1925); *J. Phys.*, **6**, 390 (1925); *Physik. Z.*, **27**, 764 (1926).

$Cab=Cab$. Where the groups a and b are complex, the dipole moment of the group may largely overshadow the effect due to the *cis* or *trans* configuration of the molecule. However, in the case of diethyl maleate ($\mu = 2.54 \times 10^{-18}$ e.s.u.) and diethyl fumarate ($\mu = 2.38 \times 10^{-18}$ e.s.u.) the *cis* form has the greater dipole moment.¹⁶ For olefins of the type $Cab=Cde$ or $Cab=Cad$, the dipole moments are not so useful in the assignment of configuration.

X-Ray Measurements (p. 1762). Debye has examined the x-ray diffraction patterns of the two dichloroethylenes.¹⁷ In the lower-melting isomer, which has been generally assigned the *cis* configuration, the distance between the chlorine atoms is 3.6 Å. In the higher-melting *trans* isomer this distance is 4.1 Å. Thus, x-ray measurements also confirm the configurations which were assigned on the basis of the other physical properties.

Other Physical Constants (p. 1720). The density,¹⁸ molecular refraction,¹⁹ molecular dispersion,¹⁹ absorption spectra,²⁰ Raman spectra,²¹ parachor,²² and other constants for *cis-trans* isomers have been studied, and sometimes they aid in assigning definite configurations to the isomers. However, these measurements are less useful than the ones which have been discussed above.

Kinetic Studies. Recently studies on the rates of reactions involving *cis* and *trans* isomers have been used to establish configuration. Wright²³ found that *cis*-methyl cinnamate was mercurated about three times as fast as the *trans* form, and that *cis*-stilbene was mercurated readily while the *trans* isomer was not. Using these facts for comparison, Thomas and Wetmore²⁴ mercurated the isomeric 2-butenes and on the basis of reaction rates assigned the *trans* configuration to the isomer which melts at -108.8° .

¹⁶ Smyth and Walls, *J. Am. Chem. Soc.*, **53**, 527 (1931).

¹⁷ Debye, *Physik. Z.*, **31**, 142 (1930).

¹⁸ von Auwers and Harres, *Z. physik. Chem.*, **143**, 1 (1929); Wassermann, *Ber.*, **63**, 559 (1930).

¹⁹ von Auwers and co-workers, *Ber.*, **54**, 624 (1921); **56**, 724 (1923); **57**, 437, 446 (1924); *Ann.*, **432**, 46, 94 (1923); Chavanne, *Rev. gén. sci.*, **35**, 333 (1924); Bruylants, *Bull. soc. chim. Belg.*, **39**, 572 (1930).

²⁰ Errera and Henri, *Compt. rend.*, **181**, 548 (1925); Errera, *J. Phys. Radium*, (VI) **7**, 215 (1926); Bruylants and Castille, *Acad. roy. Belg.*, **8**, 130 (1925); **13**, 767 (1927); Bruylants, *Bull. soc. chim. Belg.*, **39**, 572 (1930); Ramart-Lucas and Hoch, *Compt. rend.*, **189**, 696 (1929); *Ann. chim.*, [10] **13**, 385 (1930); Stobbe, *Ber.*, **43**, 504 (1910); Baly and Tuck, *J. Chem. Soc.*, **93**, 1902 (1908); Baly and Schaefer, *ibid.*, **93**, 1812 (1908).

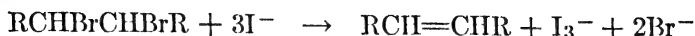
²¹ Piaux, *Ann. chim.*, [11] **4**, 167 (1935).

²² Semeria and Ribotti-Lissone, *Gazz. chim. ital.*, **60**, 862 (1930); Sugden and Whitaker, *J. Chem. Soc.*, **127**, 1868 (1925).

²³ Wright, *J. Am. Chem. Soc.*, **57**, 1993 (1935).

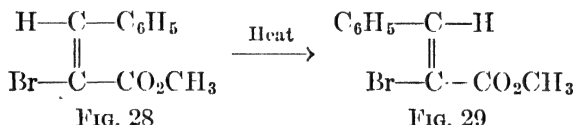
²⁴ Thomas and Wetmore, *ibid.*, **63**, 136 (1941).

meso-Dibromobutane and *meso*-dibromosuccinic acid react with iodide ion faster than the corresponding *dl*-isomers.²⁵ The reaction involved is

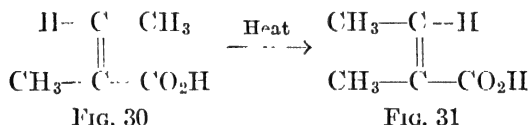


Young²⁶ studied the rates of reaction of a large number of isomeric ethylene dibromides with potassium iodide and found that the *meso*-dibromides (from the *trans* compounds) reacted more rapidly than the corresponding *dl*-dibromides (from the *cis* compounds). Rate studies of this type may be used as a means of identifying *cis-trans* isomers.

Interconversion of *cis-trans* Isomers. Usually, one of the isomers of a *cis-trans* pair is a labile form and can be readily changed into the more stable isomer by the action of heat or a variety of chemical agents. For example, heat converts maleic acid into fumaric acid;²⁷ methyl *cis*- α -bromocinnamate (Fig. 28) into methyl *trans*- α -bromocinnamate²⁸



(Fig. 29); and angelic acid (Fig. 30) into tiglic acid²⁹ (Fig. 31). In most of the isomers that have been examined, the *cis* form is the labile and the *trans* form the stable one. This agrees with the usual difference in energy



content shown by the heat of combustion data for the isomers in this series. (See Table I.)

If the stability of the two isomers is about equal, mixtures of the *cis* and *trans* forms are produced when either compound is treated with agents which cause inversion. Thus, heating the *cis* compound (Fig. 32) causes only partial conversion to the *trans* compound (Fig. 33), and



²⁵ Van Duin, *Rec. trav. chim.*, **43**, 341 (1924); **45**, 345 (1926); Dillon, Young, and Lucas *J. Am. Chem. Soc.*, **52**, 1953 (1930).

²⁶ Young, Pressman, and Coryell, *J. Am. Chem. Soc.*, **61**, 1640 (1939).

²⁷ Tanatar, *Ann.*, **273**, 32 (1893); Höjendahl, *J. Phys. Chem.*, **28**, 758 (1924).

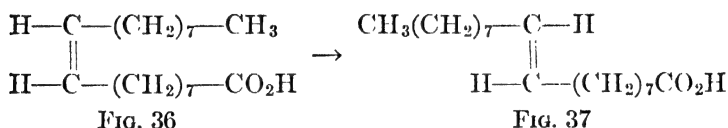
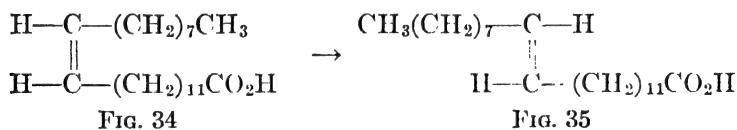
²⁸ Anschütz, *Ber.*, **20**, 1383 (1887).

²⁹ Blaise, *Ann. chim. phys.*, [8] **11**, 111 (1907).

heating the *trans* compound with iodine also gives a mixture of the two isomers.³⁰

The effect of exposure to sunlight often parallels the action of heat, but ultra-violet light, by the addition of energy to the stable form, transforms it into the labile modification. Thus, exposure of fumaric acid to ultra-violet light converts it into maleic acid.³¹ This general procedure is often the best method for obtaining the labile form, since the product of a chemical reaction is usually the stable modification.

Small amounts of various chemical agents also promote the interconversion of isomers. It is probable that only substances which can add to the double linkage can effect the transformation. The halogens and halogen acids are the most widely used reagents. Traces of iodine and sunlight are catalysts for the conversion of maleic ester into fumaric ester³² and *cis*-cinnamic acid into *trans*-cinnamic acid.³³ Boiling with aqueous solutions of any of the halogen acids converts maleic into fumaric acid,³⁴ citraconic acid into mesaconic acid,³⁵ and *cis*- α -methylglutaconic acid into *trans*- α -methylglutaconic acid.³⁶ Nitric and nitrous acids can also be used; the latter converts erucic acid (Fig. 34) into brassidic acid³⁷ (Fig. 35), and oleic acid (Fig. 36) into elaidic acid³⁸ (Fig. 37). Phosphorus pentachloride converts maleic acid into fumaryl chloride, which, on hydrolysis, yields fumaric acid.³⁹



Skraup made the interesting observation that neither sulfur dioxide nor hydrogen sulfide alone was able to cause the transformation of maleic acid into fumaric acid, but, when aqueous solutions of the two were added

³⁰ Dufraisse, *Compt. rend.*, **158**, 1691 (1914).

³¹ Stoermer, *Ber.*, **42**, 4865 (1909); Warburg, *Ber. Berl. Akad.*, 960 (1919).

³² Anschütz, *Ber.*, **12**, 2282 (1879).

³³ Berthoud and Béranek, *J. chim. phys.*, **24**, 213 (1927); Berthoud and Urech, *ibid.* **27**, 291 (1930).

³⁴ Skraup, *Monatsh.*, **12**, 118 (1891).

³⁵ Kekulé, *Ann., Spl.*, **2**, 94 (1863).

³⁶ Feist and Pomme, *Ann.*, **370**, 67 (1909).

³⁷ Rankoff, *J. prakt. Chem.*, **131**, 293 (1931).

³⁸ Grün, "Analyse der Fette und Wachse," Springer, Berlin (1925), Vol. I, p. 239.

³⁹ Perkin, *Ber.*, **14**, 2548 (1881).

to maleic acid, conversion to the *trans* isomer did occur.⁴⁰ The conversion appears to be due to the presence of finely divided sulfur, since the addition of acid to a solution of maleic acid containing sodium thiosulfate also causes the formation of fumaric acid.⁴¹

Various theories have been advanced to account for this catalytic effect of halogens, halogen acids, etc., in the conversion of *cis* to *trans* isomers. Usually the explanation has involved addition of the catalyst to the double bond and subsequent removal of the catalyst to regenerate the double bond. The most serious objection to any such theory is that, in general, the products of addition of these catalytic agents to an olefin are stable and should not be decomposed under the conditions which produce the transformation of one isomer to the other.

Olson⁴² has pointed out that the conversion of *cis*-dibromoethylene to *trans*-dibromoethylene by the catalytic action of bromine and heat is very closely related to the Walden inversion which has so often been observed in optically active molecules in reactions which involve groups attached to an asymmetric carbon atom. According to Olson's views, the conversion of *cis*-dibromoethylene (Fig. 38) to *trans*-dibromoethylene

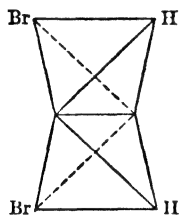


FIG. 38

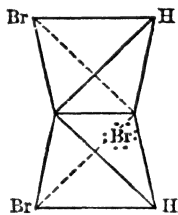


FIG. 39

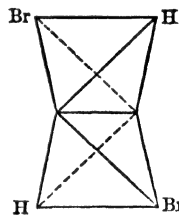


FIG. 40



(Fig. 40) would alter the configuration of one of the atoms carrying the double bond. This change is brought about by a bromide ion colliding with one of the carbon atoms held by the double bond at a point on the face of the tetrahedron opposite the apex occupied by the bromine atom (Fig. 39). This particular position on the face of the tetrahedron opposite the apex occupied by the bromine atom is the easiest point of approach for the entering bromide ion because the sphere of influence of the carbon-bromine bond in the olefin molecule extends backward to this point. When the bromide ion strikes this face of the tetrahedron, the bromine atom originally attached to the apex opposite the point of collision can move away from its point of attachment, and the tetrahedron will re-form with the new bromine atom on the opposite side of the mole-

⁴⁰ Skraup, *Monatsh.*, **12**, 108 (1891).

⁴¹ Freundlich and Schikorr, *Kolloidchem. Beihefte* **22**, 1 (1926).

⁴² Olson, *J. Chem. Phys.*, **1**, 418 (1933).

cule. Naturally, this change may go in either direction, but the tendency will be to produce, in the end, the more stable or *trans* isomer.

This theory of Olson is very attractive for the inversion discussed, where the catalyst is made up of particles which are like those attached to one carbon atom concerned in the interconversion, but it does not cover those where the reagent which causes inversion is entirely different from the groups in the olefin. A more general theory must be sought to account for these interconversions.

At the present time the best general mechanism⁴³ which can be advanced to account for the interconversion of isomers is one which involves a polarization of the double bond, such as Carothers has postulated as taking place in the preliminary stage of an addition reaction involving a double bond.⁴⁴

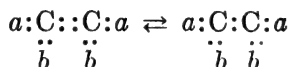


FIG. 41

FIG. 42

This unbalanced molecule (Fig. 42) is probably produced by a collision between one of the catalyst molecules (Fig. 43) and the olefin, resulting in a transitory double molecule (Fig. 44). Then the bombarding catalyst molecule drops away from the carbon atom, and the polarized double bond (Fig. 45) comes into existence for a short time. In this molecule the carbon atom which is deficient in electrons is unbalanced,

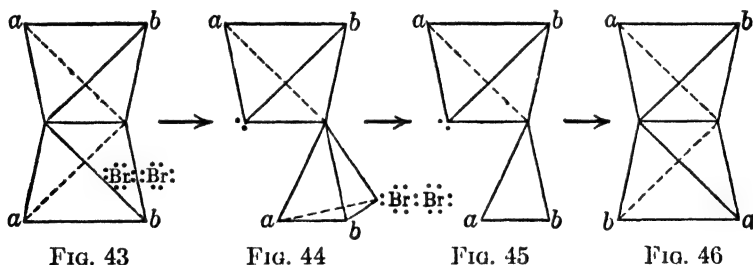


FIG. 43

FIG. 44

FIG. 45

FIG. 46

and the vibration of the positive nucleus will be of such a nature as to make the atom essentially planar. When the tetrahedral nature of this carbon atom is lost, there is just as much chance for the double union to form and produce the *trans* isomer (Fig. 46) as there is for it to produce the original *cis* isomer. Moreover, since the *trans* isomer is fundamen-

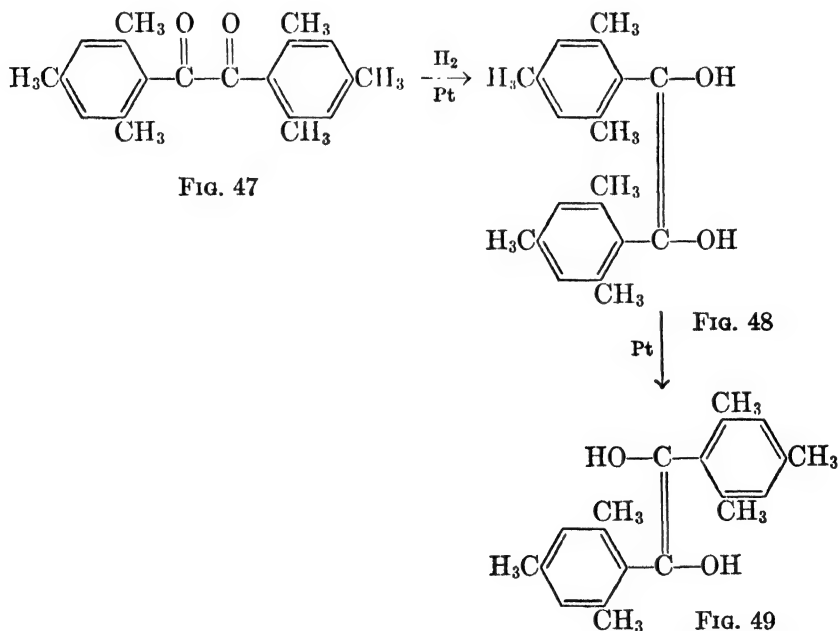
⁴³ Berthoud and Urech, *J. chim. phys.*, **27**, 291 (1930).

⁴⁴ Carothers, *J. Am. Chem. Soc.*, **46**, 2226 (1924).

tally the more stable, the molecules which are formed with this configuration will eventually be the only ones in the reaction mixture.

The rates of thermal isomerization of several *cis-trans* isomers in the gas phase were studied by Kistiakowsky⁴⁵ and by Jones.⁴⁶ The isomerization was found to be homogeneous and of the first order over a range of 566–608° K. in the case of *trans*-dichloroethylene. The mechanism proposed for such reactions was activation of the carbon-carbon double bond to form a single bond with two free valences, free rotation, inversion at one carbon atom, and again formation of a double bond.

A new and interesting example of *cis-trans* isomerism is furnished by the stilbenediols of which 2,2',4,4',6,6'-hexamethylstilbenediol is an example.⁴⁷ Catalytic hydrogenation of mesitol (Fig. 47) produced either the *cis* or *trans* form, depending on how long the treatment was continued. The *cis* or low-melting isomer (Fig. 48) was always formed first and slowly isomerized to the *trans* isomer (Fig. 49) under the influence of



hydrogen and platinum. The pure *cis* form was converted to the *trans* form merely by shaking it with platinum catalyst, which represents an interesting catalytic conversion of a *cis* to a *trans* isomer.

⁴⁵ Kistiakowsky and Nelles, *ibid.*, **54**, 2208 (1932); Kistiakowsky and Smith, *ibid.* **56**, 638 (1934); **57**, 269 (1935); **58**, 766, 2428 (1936).

⁴⁶ Jones and Taylor, *ibid.*, **62**, 3480 (1940).

⁴⁷ Fuson, Scott, Horning, and McKeever, *ibid.*, **62**, 2091 (1940).

Lutz ⁴⁸ has made a systematic study of the effect of substitution on the stability of the geometric forms of β -aroxyacrylic acids. The formation and reactions of lactones and lactamols in the *cis* acids and amides have also been investigated. Lutz found that a methyl group on the 3-carbon atom of the acrylic acid stabilized the *cis* form better than a methyl group on the 2-carbon atom and that methyl groups on both the 2- and 3-positions made the *cis* form very stable.

The compound made by esterification with methyl iodide of the silver salt of the acid obtained by the action of benzene on maleic anhydride was identical with the compound made by the action of benzene on the monomethyl ester acid chloride of fumaric acid. Inversion had taken place in the case of the maleic anhydride to give the *trans* acrylic ester, Fig 50, indicating it to be the stable form.

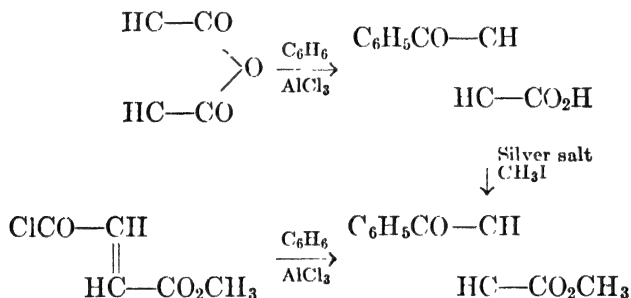
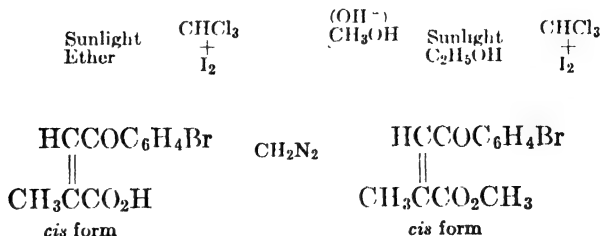
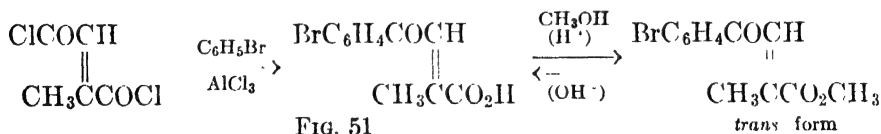


FIG. 50

Isomerizations of 3-(*p*-bromobenzoyl)-2-methylacrylic acid (Fig. 51) and 3-benzoyl-2,3-dimethylacrylic acid (Fig. 52) are summarized in the following charts:



⁴⁸ Lutz and others, *ibid.*, **52**, 3423 (1930); **55**, 1168, 1585, 1593 (1933); **56**, 445, 1378 (1934); *J. Org. Chem.*, **4**, 95 (1939); **6**, 77, 91, 175 (1941).

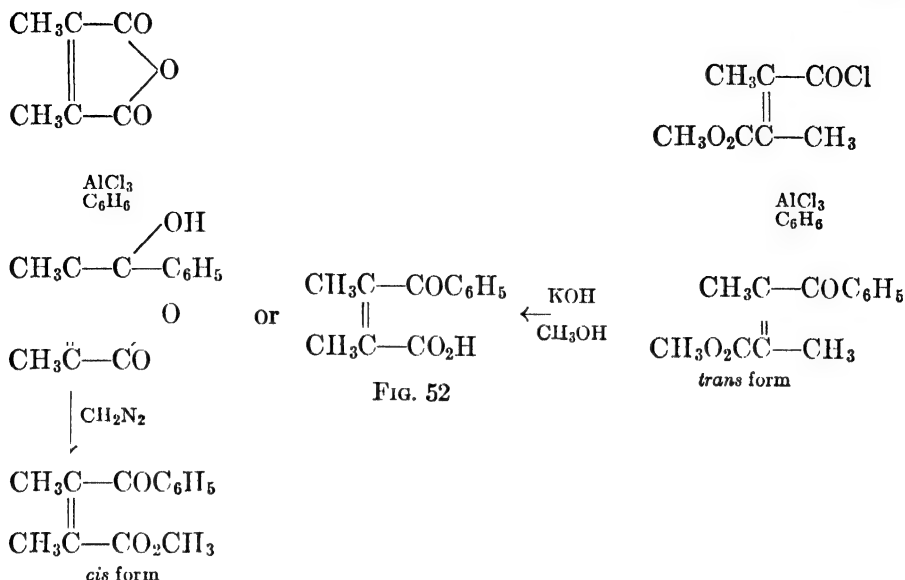


FIG. 52

Chemical Behavior of *cis-trans* Isomers. It has already been mentioned that *cis* isomers can often be converted to ring compounds more readily than can the *trans* isomers. There are other reactions in which the isomers show distinct differences in their behavior.

Sunlight will cause the two cinnamic acids to dimerize, giving cyclobutane derivatives. *trans*-Cinnamic acid (Fig. 53) gives truxillic acids

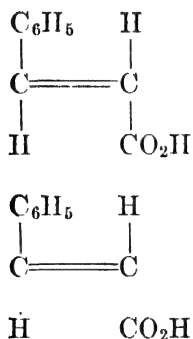


FIG. 53

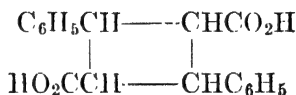


FIG. 54

(Fig. 54), whereas *cis*-cinnamic acid (Fig. 55) gives truxinic acids (Fig. 56).⁴⁹

⁴⁹ Stoermer and co-workers, *Ann.*, **342**, 1 (1905); *Ber.*, **42**, 4865 (1909); **44**, 639 (1911); **45**, 3099 (1912); **46**, 1249 (1913); **47**, 1786 (1914); **55**, 1030 (1922); Stobbe, *Ber.*, **58**, 2415 (1925); Shemyakin, *Compt. rend. acad. sci. U.R.S.S.*, **29**, 199 (1940).

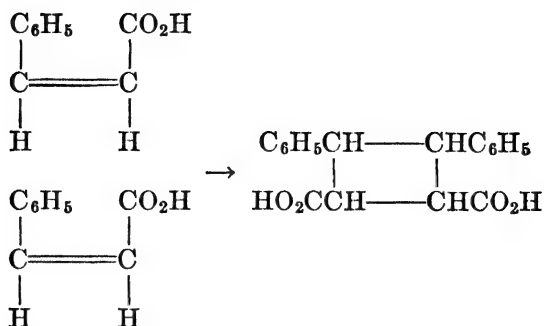


FIG. 55

FIG. 56

Relationship of Olefins to Acetylenes. Wislicenus pointed out that the addition of groups to an acetylene (Fig. 57) should theoretically produce a *cis* isomer of the olefin type ⁵⁰ (Fig. 58).

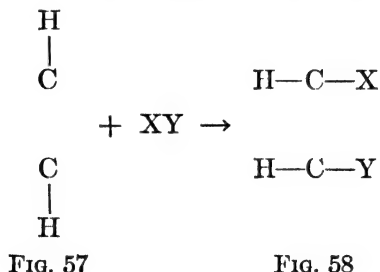
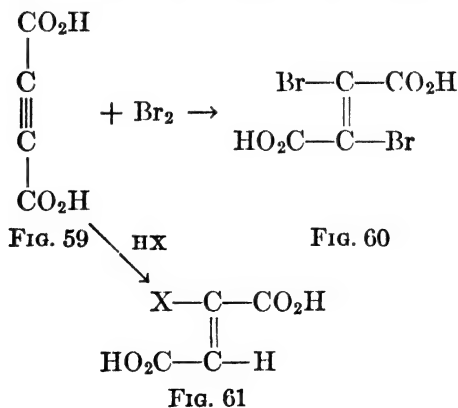


FIG. 57

FIG. 58

In actual practice this theory has been found not to be valid. Michael showed that addition of bromine to acetylenedicarboxylic acid (Fig. 59) produced mainly dibromofumaric acid ⁵¹ (Fig. 60), and halogen acids gave halofumaric acids (Fig. 61) rather than maleic acid derivatives. ⁵²



⁵⁰ Wislicenus, *Abhandl. sächs. Ges. Wiss.*, **14**, I (1887) [*Chem. Zentr.*, 1005 (1887)]

⁵¹ Michael, *J. prakt. Chem.*, **46**, 210 (1892).

⁵² Michael, *ibid.*, **52**, 321 (1895).

Catalytic reduction of acetylene derivatives sometimes yields *cis* and sometimes *trans* olefins, depending on the catalyst and the conditions of reduction. These results show that addition to the triple bond must involve configurational changes during addition, or inversion of olefin isomers by the catalytic effect of the adding group. The conditions which favor inversion are encountered in the conditions which favor addition of a reagent to an acetylene molecule.

It is easier to remove halogen acid from a *trans* olefinic derivative than from the *cis* isomer. Thus, halogen acid is removed from chlorofumaric acid (Fig. 62) about forty-eight times more rapidly than it is from chloromaleic acid⁵³ (Fig. 63).

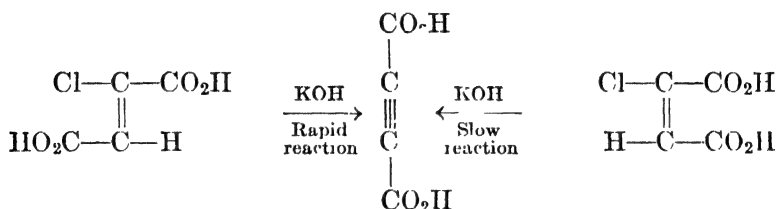


FIG. 62

FIG. 63

In the cases studied, the elimination of groups from *trans* positions takes place more readily than elimination of the same groups from the *cis* positions.

Relationship of *cis-trans* Isomers to Saturated Derivatives. The addition of hydroxyl groups to the double bonds in maleic and fumaric acids leads to the formation of tartaric acid derivatives. It is of interest that careful oxidation of maleic acid (Fig. 64) yields *meso*-tartaric acid⁵⁴ (Fig. 65),

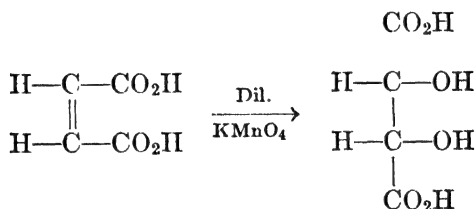


FIG. 64

FIG. 65

while under the same conditions fumaric acid (Fig. 66) yields *dl*-tartaric acid⁵⁵ (Fig. 67).

In this oxidation it is obvious that the hydroxyl groups enter the

⁵³ Michael, *ibid.*, **52**, 308 (1895).

⁵⁴ Kekulé and Anschütz, *Ber.*, **14**, 713 (1881).

⁵⁵ Kekulé and Anschütz, *Ber.*, **13**, 2150 (1880).

molecule at the same positions on the carbon tetrahedrons which were previously united in the double union, and *cis* addition has occurred.

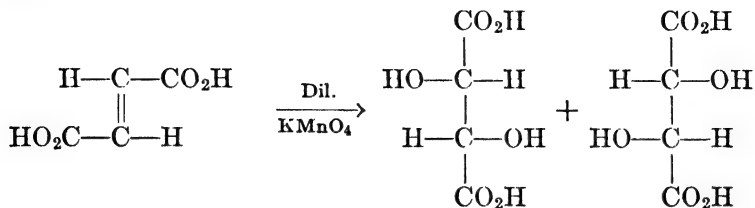
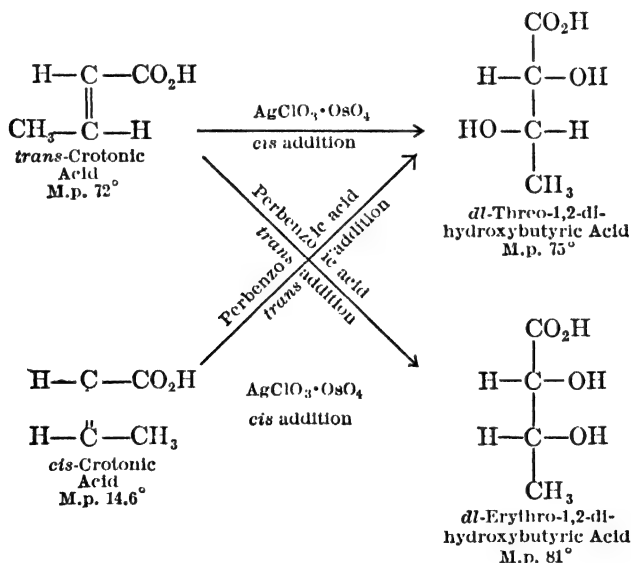


FIG. 66

FIG. 67

cis Addition, however, is not the general behavior, for bromine adds to maleic acid to give the racemic dibromosuccinic acid, whereas fumaric acid and bromine give the *meso*-dibromosuccinic acid.⁵⁶ The mechanism of the addition of bromine to the double union must be somewhat different from that of the addition of hydroxyl groups by the action of potassium permanganate.

Braun⁵⁷ has shown that the nature of the reagent and the experimental conditions used have important effects in determining whether *cis* or *trans* addition occurs when the crotonic acids are oxidized. The following chart summarizes his results:

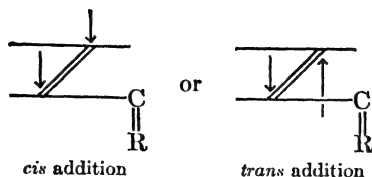


The Diels-Alder Reaction. The steric selectivity of the diene synthesis has been studied by Alder and Stein.⁵⁸ There are two possible ways in which the diene can add to the activated double bond:

⁵⁶ Terry and Eichelberger, *J. Am. Chem. Soc.*, **47**, 1067 (1925).

⁵⁷ Braun, *ibid.*, **51**, 228 (1929).

⁵⁸ Alder and Stein, *Angew. Chem.*, **50**, 510 (1937).



An example is the reaction of 1,3-butadiene with maleic acid:

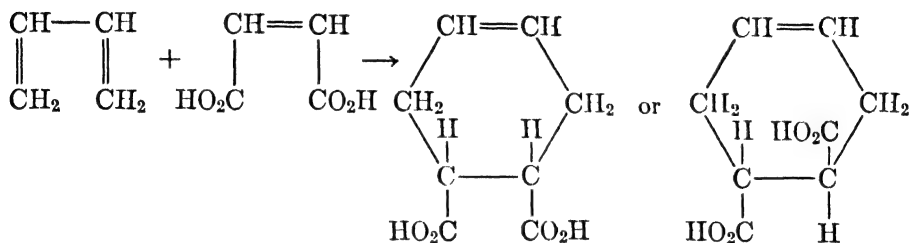


FIG. 68

FIG. 69

The *cis* acid (Fig. 68) is isolated from the reaction mixture. Proof of this is the fact that hydrogenation of the product gives the *cis*-hexahydrophthalic acid (Fig. 70). The *cis* acid does not come from rearrangement

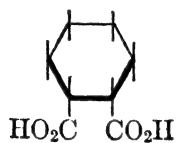


FIG. 70

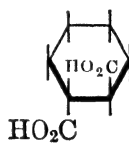


FIG. 71

of the *trans* acid during hydrogenation because if the compound represented by Fig. 68 is rearranged to that represented by Fig. 69 and then hydrogenated, the *trans*-hexahydrophthalic acid (Fig. 71) is produced.

Another example of *cis* addition is the reaction of 1,3-butadiene with 1,4-benzoquinone:

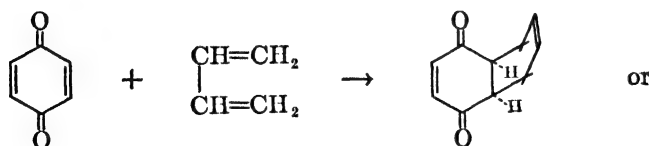


FIG. 72

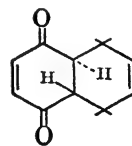
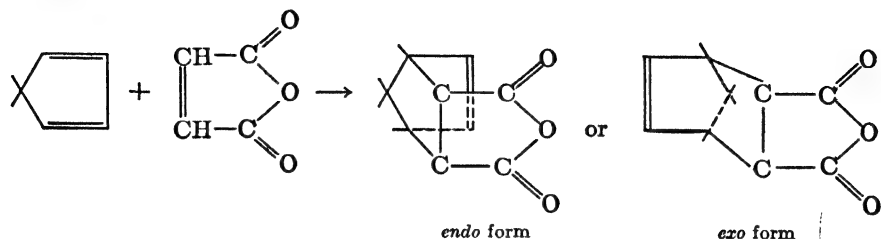


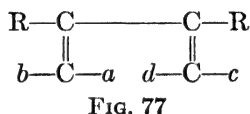
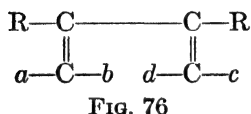
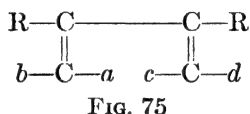
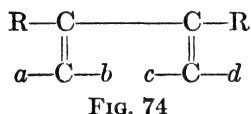
FIG. 73

The product isolated is that represented by Fig. 72, shown by the fact that hydrogenation followed by mild oxidation produces the *cis*-hexahydrophthalic acid (Fig. 70). Numerous studies have shown that pure *cis* addition always occurs in the diene synthesis.

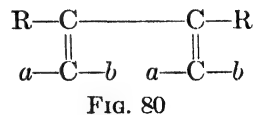
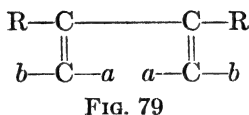
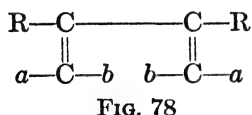
Another type of isomerism possible in diene syntheses is the *exo-endo* type. This is illustrated by the reaction product of cyclopentadiene and maleic anhydride. Actually, the *endo* form is produced in the reaction.



***cis-trans* Isomers in Polyolefins.** When more than one unsymmetrically substituted double bond is present in a molecule, the number of *cis-trans* isomers can be readily determined by writing out the possible structures. If the groups attached to the doubly bound carbon atoms are such as to make all olefin units unlike, the number of isomers possible is 2^n , where n is the number of olefin linkages. Thus, the compound $abC=CR-CR=Ccd$ can exist in four *cis-trans* forms (Figs. 74-77). However, where the substitution around the olefin



linkage is such as to make the units alike, the number of isomers is less than 2^n . For example, the compound $abC=CR-CR=Cab$ can exist in only three *cis-trans* forms (Figs. 78-80).



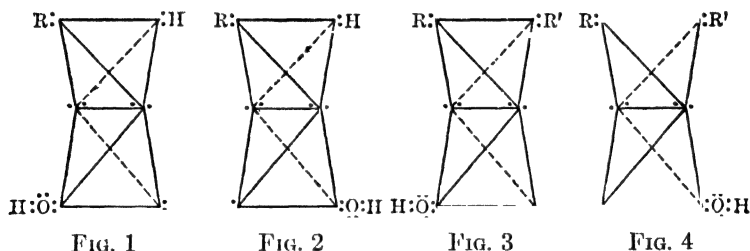
Kuhn and Winterstein⁵⁹ point out that the number of isomers in polyenes of the type, $R(CH=CH)_nR$ is equal to $2^{n-1} + 2^{p-1}$; where n is the number of double bonds. If n is even, then $p = n/2$; if n is odd, then $p = (n + 1)/2$. The synthetic and natural polyenes usually occur in only one of the possible isomeric forms.

⁵⁹ Kuhn and Winterstein, *Helv. Chim. Acta*, **11**, 87, 116, 123, 144 (1928).

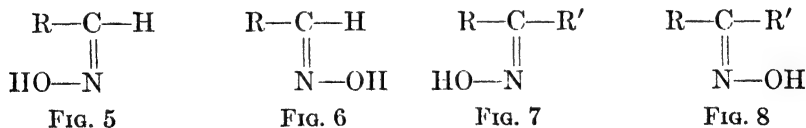
CARBON-NITROGEN DOUBLE BONDS IN OXIMES

In 1883 Goldschmidt¹ noted that benzildioxime could be converted to an isomeric compound merely by heating its alcohol solution. A short time later Beckmann² showed that benzaldoxime exists in two isomeric forms. Since that time, many examples of isomeric oximes have been recorded. In 1890, Hantzsch and Werner³ pointed out that if the three valencies of the nitrogen atom in an oxime do not lie in the same plane, there should be an analogy between the isomerism of oximes and that of *cis-trans* isomers in the olefin series. The assumption of Hantzsch and Werner has proved valid, and now, with the knowledge that the nitrogen atom is tetrahedral, the existence of *cis* and *trans* isomers in oximes is explained on exactly the same basis of restricted rotation as was used in the olefin series.*

All aldioximes and ketoximes of unsymmetrical ketones should be capable of existing in *cis* and *trans* forms (Figs. 1-4). One corner of the



nitrogen tetrahedron is occupied by an unshared pair of electrons. These compounds are usually written in the condensed form shown in Figs. 5-8.



In the nomenclature of oximes it is customary to use the prefix *syn* in place of *cis*, and *anti* in place of *trans*. In aldioximes the isomer (Fig. 6) which has the hydroxyl group of the oxime closer to the hydrogen atom on the carbon is called *syn* and the isomer (Fig. 5) in which the

¹ Goldschmidt, *Ber.*, **16**, 2176 (1883).

² Beckmann, *Ber.*, **20**, 2766 (1887).

³ Hantzsch and Werner, *Ber.*, **23**, 11 (1890).

* It should be noted that, if the nitrogen atom is tetrahedral, tertiary amines of the type $\text{R}^1\text{R}^2\text{R}^3\text{N}$ should be resolvable. However, this has never been realized experimentally (p. 402).

hydroxyl group and hydrogen are on the opposite sides of the double union is called *anti*. In the case of ketoximes, it is necessary to indicate which group of the ketone is *syn* or *anti* to the hydroxyl. The examples given below illustrate the system of naming which is in common use.

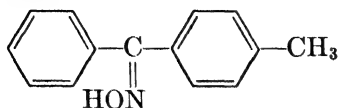


FIG. 9

syn-Phenyl *p*-tolyl ketoxime
or
anti-*p*-Tolyl phenyl ketoxime

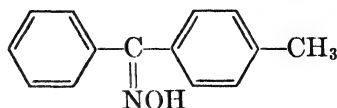


FIG. 10

syn-*p*-Tolyl phenyl ketoxime
or
anti-Phenyl *p*-tolyl ketoxime

It has been suggested that *syn* and *anti* forms of oximes are structural and not stereoisomers. The various possible structural forms which have been suggested are the following:

H

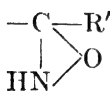


FIG. 11

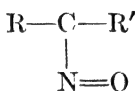


FIG. 12

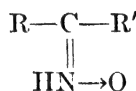


FIG. 13

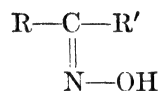


FIG. 14

The first two of these possible isomers (Figs. 11 and 12) contain asymmetric carbon atoms and should be resolvable, whereas no oximes have been obtained in which optical activity is due to the oxime grouping. The nitroso structure (Fig. 12) does not account for the known amphoteric character of the oximes.

The amine oxide type formula (Fig. 13) has received considerable attention. Actually alkylation of a symmetrical oxime often produces two isomeric products, one a nitrogen alkylated oxime which is derived from this amine oxide type, and the other an oxygen alkylated product derived from the usual oxime structure (Fig. 14).

Semper and Lichtenstadt⁴ showed that benzophenone oxime (Fig. 15) on methylation gives an N-methyl derivative (Fig. 16), and an O-methyl derivative (Fig. 17).

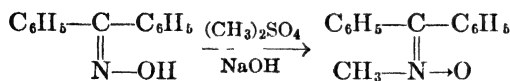


FIG. 15

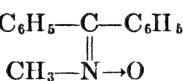


FIG. 16

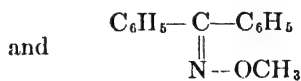
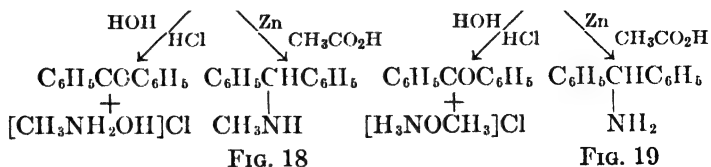


FIG. 17

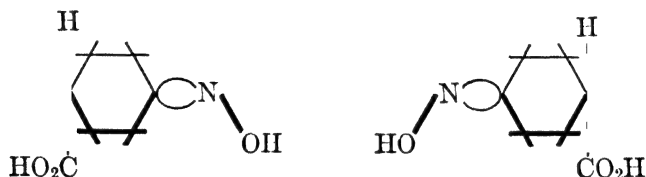


⁴ Semper and Lichtenstadt, *Ber.*, **51**, 928 (1918).

The structure of the N-methyl derivative (Fig. 16) was established by the fact that it could be hydrolyzed to give N-methylhydroxylamine and benzophenone, while reduction converted it into benzohydrylmethylamine (Fig. 18). The O-methyl derivative (Fig. 17) by hydrolysis gave O-methylhydroxylamine and by reduction benzohydrylamine (Fig. 19).

Further evidence of this has been obtained by studies of the oximes of phenyl *p*-tolyl ketone⁴ and *p*-nitrobenzophenone.⁵ These unsymmetrical ketones yield the usual *syn* and *anti* forms, each of which on alkylation gives O-alkyl and N-alkyl derivatives. Hence, the amine oxide structure does not aid in accounting for the *syn* and *anti* forms of oximes, but is necessary to account for the tautomerism of these isomers.

The non-planar nature of the trivalent nitrogen atom in an oxime was definitely proved by the resolution of the oxime of cyclohexanone-4-carboxylic acid by Mills and Bain.⁶ This oxime does not exist in *syn* and



anti forms as would be required if the three valences of the nitrogen atom were in one plane. It does exist as a racemic mixture which can be separated into its two optical isomers. The resolution of this oxime further shows that the nitroso formula (Fig. 12) is not a possibility, since 4-nitrosocyclohexane-1-carboxylic acid has a plane of symmetry.

Determination of Configuration. Assignment of configuration to oximes has been made on the basis of (1) relation of an oxime to a cyclic compound; (2) product of the Beckmann rearrangement of an oxime; (3) dipole moments of alkyl derivatives of oximes; (4) evidence for restricted rotation in certain oximes.

Relationship to Cyclic Compounds. As in the case of *cis-trans* isomers in the olefin series the best method of proving the structure of an oxime is to relate it to a cyclic compound.

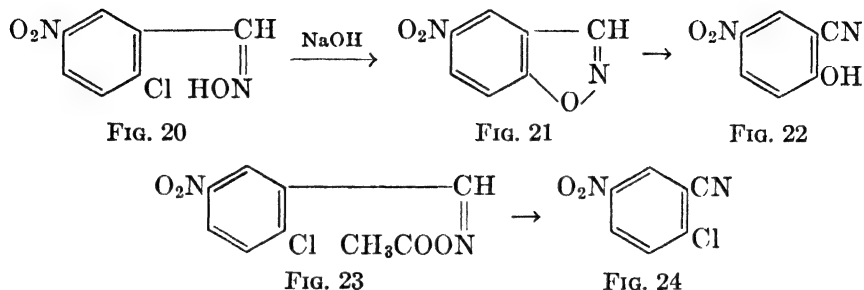
Brady and Bishop⁷ prepared two forms of 2-chloro-5-nitrobenzaloxime. These two isomers behaved differently when treated with dilute alkali and with acetic anhydride. It should be noted that the aldoxime (Fig. 20) which loses hydrogen chloride to form a cyclic molecule (Fig. 21) under the influence of alkali is the form which gives an

⁵ Brady and Mehta, *J. Chem. Soc.*, **125**, 2297 (1924).

⁶ Mills and Bain, *ibid.*, **97**, 1866 (1910).

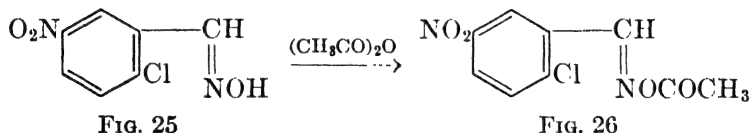
⁷ Brady and Bishop, *ibid.*, **127**, 1357 (1925).

unstable acetate (Fig. 23) with acetic anhydride; the acetate loses acetic acid readily to give the nitrile (Fig. 24). Since only the *anti* form of the aldoxime (Fig. 20) can give a cyclic compound, it must be concluded that *trans* elimination of acetic acid is the rule in the aldoxime acetate series.



The indoxazine (Fig. 21) readily rearranges to the phenolic nitrile (Fig. 22).

The *syn* form of 2-chloro-5-nitrobenzaldehyde (Fig. 25) is not converted to a cyclic molecule with dilute alkali and gives a stable acetate (Fig. 26) on treatment with acetic anhydride. This acetate can be con-



verted to the nitrile (Fig. 24), but only with difficulty, and the change apparently involves a preliminary rearrangement of *syn*-acetate (Fig. 26) to *anti*-acetate (Fig. 23).

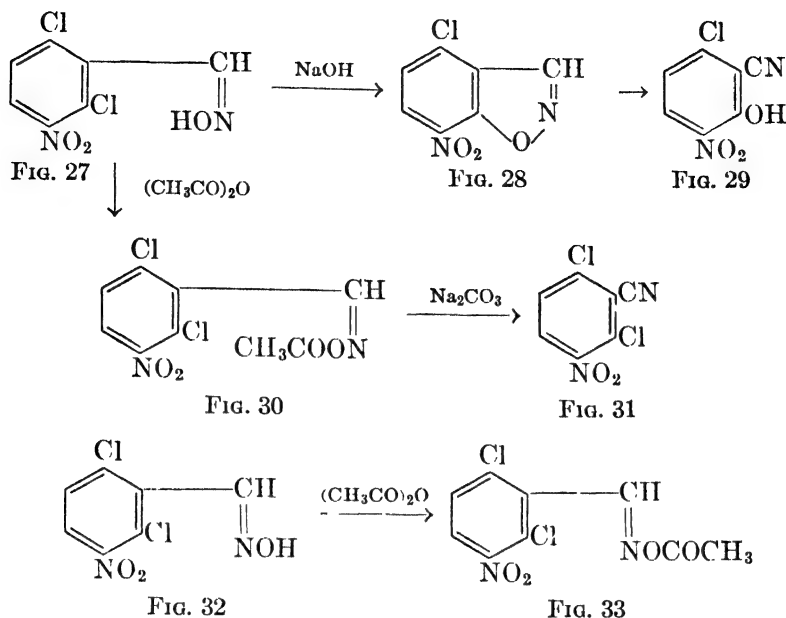
Meisenheimer⁸ made a similar study with the isomeric 3-nitro-2,6-dichlorobenzaldoximes. The *anti*-oxime (Fig. 27) gave a cyclic compound (Fig. 28) which readily rearranged to the phenolic nitrile (Fig. 29). The acetate of the oxime (Fig. 30) was unstable, and sodium carbonate converted it into the nitrile (Fig. 31), whereas the *syn*-oxime (Fig. 32) was unaffected by alkali and gave a stable acetate (Fig. 33) on treatment with acetic anhydride.*

Meisenheimer⁹ used this same general procedure to establish the structure of the *syn* and *anti* forms of 2-bromo-5-nitroacetophenone

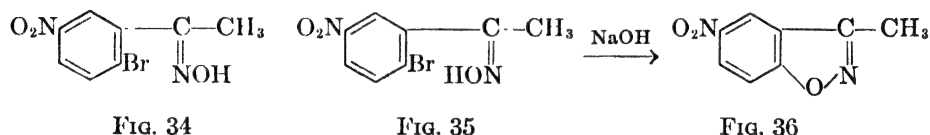
⁸ Meisenheimer, Theilacker, and Beisswenger, *Ann.*, **495**, 249 (1932).

* The literature previous to 1925 contains many errors in connection with configurational work on aldoximes, as it was then thought that the oxime which gave the unstable acetate and nitrile was the *syn* compound. In reading this earlier literature, it should be remembered that configurations are reversed in almost all cases.

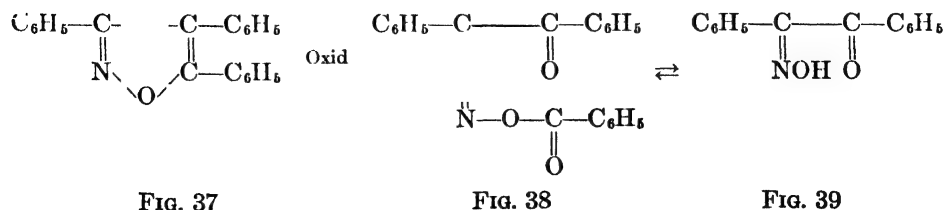
⁹ Meisenheimer, Zimmermann, and Kummer, *Ann.*, **446**, 205 (1926).



oxime. The α -oxime, melting at 171° , is unaffected by alkali and must, therefore, be *syn* with respect to the hydroxyl group and the methyl group (Fig. 34). The β -oxime, m. p. 132° , gives an indoxazine (Fig. 36) on treatment with alkali, and hence is *syn* with respect to the hydroxyl group and phenyl group (Fig. 35).

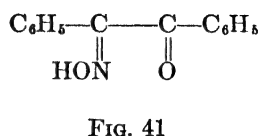
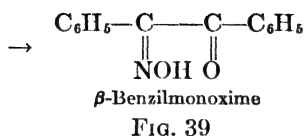
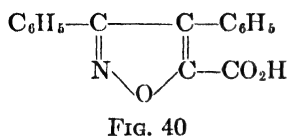


In 1921 Meisenheimer¹⁰ oxidized 3,4,5-triphenylisoxazole (Fig. 37) and obtained the benzoyl derivative (Fig. 38) of the benzilmonoxime having the hydroxyl *anti* with respect to the phenyl group. This benzoyl derivative was hydrolyzed to the free oxime (Fig. 39) which, on benzoylation, gave the original acyl derivative again.

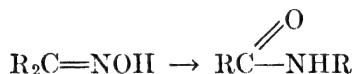


¹⁰ Meisenheimer and Weibezahn, *Ber.*, **54**, 3195 (1921).

In 1924, Kohler¹¹ ozonized 3,4-diphenyl-5-carboxyisoxazole (Fig. 40) and obtained the same monoxime of benzil (Fig. 39). This form had previously been named the β -monoxime of benzil. The second isomer, called the α -monoxime of benzil, must have the *syn*-phenyl configuration (Fig. 41).



The Beckmann Rearrangement (p. 979). In 1886, Beckmann¹² treated benzophenone oxime with phosphorus pentachloride and after decomposing the reaction mixture with water isolated benzanilide. This rearrangement of ketoximes to substituted amides



is a very general reaction and may be brought about by a variety of reagents, such as phosphorus pentachloride,¹² phosphorus oxychloride,^{12, 13} acetyl chloride,¹⁴ benzenesulfonyl chloride,¹⁵ acetic anhydride containing hydrochloric acid,¹⁴ sulfuric acid,¹⁶ and many metallic chlorides.¹⁷

Early work showed that the isomeric forms of a ketoxime led to isomeric amides. The reaction became a reliable method for determining the configuration of ketoximes when Meisenheimer (see above) definitely established the structure of β -benzilmonoxime (Fig. 42) and showed that it produced the anilide of benzoylformic acid (Fig. 43) in the Beckmann rearrangement.

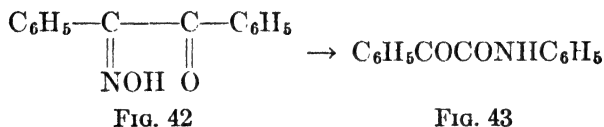


FIG. 43

¹¹ Kohler, *J. Am. Chem. Soc.*, **46**, 1733 (1924).

¹² Beckmann, *Ber.*, **19**, 988 (1886).

¹³ Beckmann, *Ber.*, **27**, 300 (1894).

¹⁴ Beckmann, *Ber.*, **20**, 2580 (1887).

¹⁵ Wege, *Ber.*, **24**, 3537 (1891); Werner and Detscheff, *Ber.*, **38**, 69 (1905).

¹⁶ Beckmann, *Ber.*, **20**, 1507 (1887); **27**, 300 (1894).

¹⁷ Beckmann and Bark, *J. prakt. Chem.*, **105**, 342 (1923); Lehmann, *Z. angew. Chem.*, **36**, 360 (1923); Lachman, *J. Am. Chem. Soc.*, **46**, 1477 (1924); **47**, 260 (1925).

Also, α -benzilmonoxime (Fig. 44) of established configuration gave dibenzoylimide (Fig. 45) by rearrangement.¹⁸

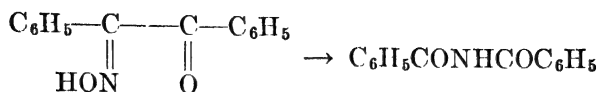
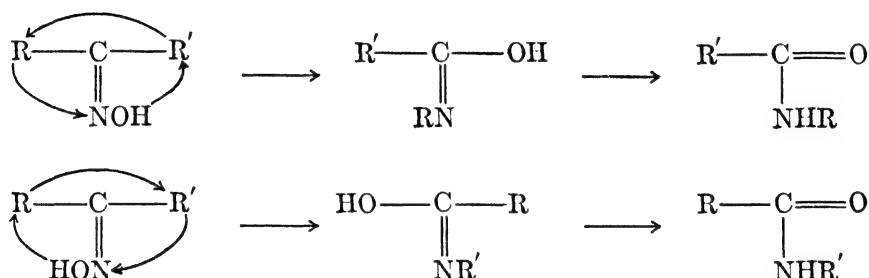


FIG. 44

FIG. 45

Meisenheimer pointed out that the oxime hydroxyl group moves up to occupy the space on the carbon atom previously filled by the *syn* R group, whereas the *anti* R group moves to the nitrogen atom. The following scheme was used to aid in visualizing the transformations:



In the earlier literature there are many mistaken interpretations of data obtained by Beckmann rearrangements of ketoximes due to an old belief that the *syn* groups (OH and R) merely exchanged their positions. At present the only serious limitation to this method of determining the configuration of ketoximes is that certain aliphatic ketoximes give both amides owing to ready interconversion of the two forms of the oxime.¹⁹

Dipole Moments of Oxime Derivatives. Sutton and Taylor²⁰ measured the dipole moments (p. 1752) of a number of O- and N-methyl ethers of the oxime of *p*-nitrobenzophenone, and were able to correlate some of their results with those obtained by the Beckmann rearrangement. However, as a method of determining configuration, this physical measurement is still unsatisfactory.

Restricted Rotation. Meisenheimer²¹ prepared two isomeric oximes of 1-aceto-2-hydroxy-3-carboxynaphthalene (Figs. 46 and 47) and found that one form of the oxime (β) gives salts with coniine, cinchonine, and strychnine which exhibit mutarotation in pyridine, indicating that the oxime molecule is asymmetric. The N-methyl ether of the β -oxime

¹⁸ Meisenheimer, *Ber.*, **54**, 3206 (1921).

¹⁹ Sutton and Taylor, *J. Chem. Soc.*, 2190 (1931); Blatt, *Chem. Rev.*, **12**, 215 (1933).

²⁰ Sutton and Taylor, *J. Chem. Soc.*, 2190 (1931).

²¹ Meisenheimer, Theilacker, and Beisswenger, *Ann.*, **495**, 249 (1932).

(Fig. 48) was obtained in two optically active forms. The existence of optical isomers of this oxime or its ether can be explained on the basis of restricted rotation similar to that observed in the *ortho* substituted biphenyls. Restricted rotation would be expected in the oxime in which the hydroxyl group is *syn* to the naphthalene nucleus (Fig. 47). The α -oxime could not be resolved, and its alkaloid salts showed no mutarotation. Its configuration must, therefore, be that with the

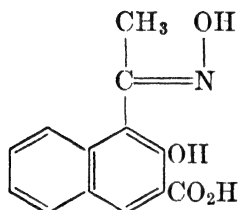


FIG. 46

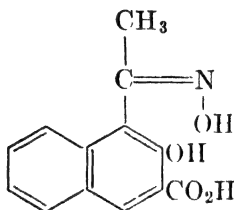


FIG. 47

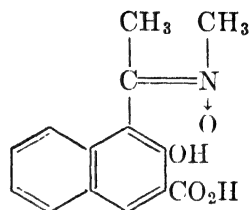
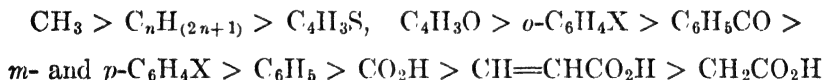


FIG. 48

oxime hydroxyl group *anti* to the naphthalene nucleus (Fig. 46). The products from the Beckmann rearrangement of these two oximes are those which would be predicted from the configurations assigned to the oximes on the basis of the resolution experiments.

Interconversion of *syn*- and *anti*-Oximes. When an aldehyde or unsymmetrical ketone is treated with hydroxylamine, the two possible forms of the oxime do not always result. Usually in the aliphatic series only one form can be isolated. Most of the known pairs of isomers have been obtained from aromatic aldehydes and ketones. Hantzsch²² studied the configurations of a large number of oximes. He arranged the following series of R groups on the basis of their attraction for the hydroxyl group of the oxime.



Thus, in an oxime prepared from a ketone $\text{C}_6\text{H}_5\text{COR}$ the *syn*-R form (Fig. 49) is stable if R comes before phenyl, and the *anti*-R form (Fig. 50) is stable if R follows phenyl in the above series.

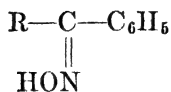


FIG. 49

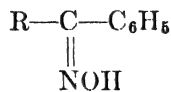


FIG. 50

Many reagents convert the labile oxime into the stable form. Bromine, acids, and bases have been used extensively for this purpose. Heat

²² Hantzsch, *Ber.*, **25**, 2164 (1892).

usually converts the labile isomer to the stable; ultra-violet light often converts the stable form to the labile one.

Other Carbon-Nitrogen Double Bonds. It is evident that any molecule containing the $>C=N-$ group should be capable of existing in *syn-anti* forms. As a matter of fact, isomers have actually been obtained in a considerable number of cases. For example, Fehrlin¹ and Krause² obtained two isomeric phenylhydrazones from *o*-nitrophenylglyoxylic acid; Overton³ obtained isomeric diphenylhydrazones from phenyl *p*-tolyl ketone; Hopper⁴ obtained isomeric monosemicarbazones from benzil; Stieglitz and his students⁵ obtained isomeric chloroimides of the type shown in Figs. 1 and 2, and Manchot and Furlong⁶ reported *syn* and *anti* forms of certain Schiff's bases.

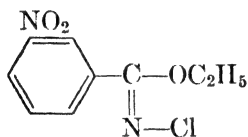


FIG. 1

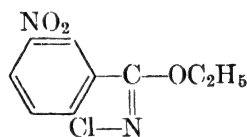
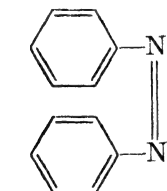


FIG. 2

This general field has not been so intensively studied as the olefins and oximes.

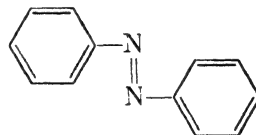
NITROGEN-NITROGEN DOUBLE BONDS

A logical extension of the tetrahedral nitrogen structure leads to the prediction that *syn-anti* isomers should be encountered in compounds of the type $A-N=N-A$ or $A-N=N-B$. The simplest example of this type of isomerism has been furnished by the isolation of the *cis* and *trans* forms of azobenzene. (Figs. 1 and 2).



cis or *syn* form

FIG. 1



trans or *anti* form

FIG. 2

¹ Fehrlin, *Ber.*, **23**, 1574 (1890).

² Krause, *Ber.*, **23**, 3617 (1890).

³ Overton, *Ber.*, **26**, 32 (1893).

⁴ Hopper, *J. Chem. Soc.*, **127**, 1282 (1925).

⁵ Stieglitz and Earle, *Am. Chem. J.*, **30**, 399 (1903); Stieglitz, *ibid.*, **40**, 36 (1908) Hilpert, *ibid.*, **40**, 150 (1908); Stieglitz and Peterson, *Ber.*, **43**, 782 (1910); Peterson, *Am Chem. J.*, **46**, 325 (1911).

⁶ Manchot and Furlong, *Ber.*, **42**, 3030 (1909).

Azobenzene prepared by oxidation of hydrazobenzene or reduction of azoxybenzene is always isolated as the *trans* form, which melts at 68°. Recently Hartley¹ succeeded in isolating the *cis* form of azobenzene. An acetic acid solution of ordinary azobenzene was exposed to sunlight for some time, water added, and the mixture filtered. Extraction of the aqueous filtrate with chloroform gave *cis*-azobenzene, which melted at 71.4°. The *cis* form had a dipole moment of 3.0 Debye units in contrast to a zero dipole moment for the *trans* form.²

Hartley has also studied the equilibrium $cis \rightleftharpoons trans$ in various solvents and has found that from 15 to 40 per cent of the *cis* isomer is present in solutions exposed to sunlight. The conversion has an activation energy of 23 kcal., and two values are given for the heat of conversion, 12 kcal. per g. mole by Hartley, and 9.9 kcal. per g. mole by Corruccini and Gilbert.³

The two forms of azobenzene and other azo compounds have also been separated by chromatographic adsorption. Aluminum oxide was used as the adsorbent and petroleum ether or benzene as the solvent.⁴

Freundlich and Heller⁵ found that the *cis* form was more strongly adsorbed on alumina than the *trans* form, especially from petroleum ether solution. The *trans* form is more strongly adsorbed on charcoal from methanol solution.

von Auwers has substantiated the *cis* nature of the new form by spectrochemical methods.⁶

Euler and Hantzsch⁷ observed that treatment of *p*-methoxybenzenediazonium chloride (Fig. 3) with sodium cyanide produced at first a true diazonium cyanide (Fig. 4) which gradually isomerized to

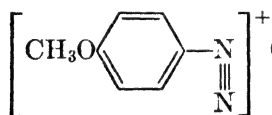


FIG. 3

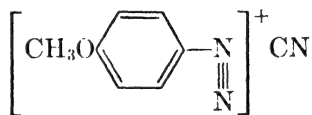


FIG. 4

give a mixture of two products which they showed to be the *syn* (Fig. 5) and *anti* (Fig. 6) forms of the corresponding diazocyanide.

The diazonium cyanide (Fig. 4) is a colorless salt, soluble in water, and gives a solution which is a good conductor of electricity. The *syn*-

¹ Hartley, *Nature*, **140**, 281 (1937); *J. Chem. Soc.*, 633 (1938).

² Hartley and Le Fèvre, *J. Chem. Soc.*, 531 (1939).

³ Corruccini and Gilbert, *J. Am. Chem. Soc.*, **61**, 2925 (1939).

⁴ Cook, *J. Chem. Soc.*, 876 (1938); Cook and Jones, *ibid.*, 1309 (1939); Zechmeister, Frehdén, and Jörgensen, *Naturwissenschaften*, **26**, 495 (1938).

⁵ Freundlich and Heller, *J. Am. Chem. Soc.*, **61**, 2228 (1939).

⁶ von Auwers, *Ber.*, **71**, 611 (1938).

⁷ Euler and Hantzsch, *Ber.*, **34**, 4166 (1901).

and *anti*-diazocyanides are colored, insoluble in water, soluble in organic solvents, can be hydrolyzed with water to give amides, and react with

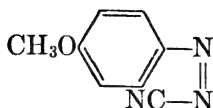


FIG. 5

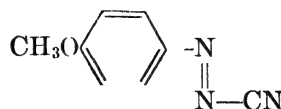


FIG. 6

ammonia to give amidines and with alcohols to give imido esters. Many such pairs of *syn*- and *anti*-diazocyanides have been recorded in the literature.

The best evidence that these diazocyanides are *cis-trans* isomers has been furnished by showing that the addition of reagents to the nitrogen-nitrogen double bond destroys the isomerism. Thus, either *syn*- or *anti*-*p*-chlorobenzene diazocyanide ⁸ (Figs. 7 and 8) give the same addition product (Fig. 9) with benzenesulfonic acid.

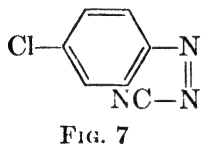


FIG. 7

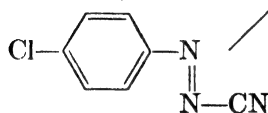


FIG. 8

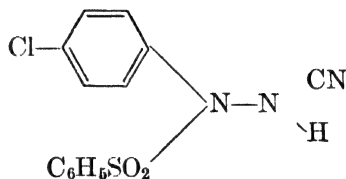


FIG. 9

Stephenson and Waters ⁹ extended the study of diazocyanides to those derived from halogenated aromatic amines. It was found that *anti*-diazocyanides were thermally stable, but could be transformed photochemically into the reactive *syn* isomers.

If silver nitrate is added to an alcoholic solution of a *syn*-diazocyanide, silver cyanide is produced, whereas no reaction with silver nitrate is observed with the *anti* isomer unless it is converted to the *syn* form by exposure to light. Solutions of *syn*-diazocyanides in non-ionizing solvents isomerize to the *anti* forms even in the absence of light. These facts are expressed in the following equilibria:



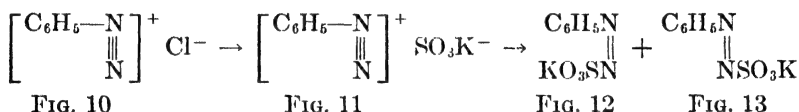
⁸ Hantzsch and Glogauer, *Ber.*, **30**, 2548 (1897).

⁹ Stephenson and Waters, *J. Chem. Soc.*, 1796 (1939).

If solutions of the *syn*-diazocyanides in non-ionizing solvents such as carbon tetrachloride, benzene, and ether are warmed, no nitrogen is evolved although a conversion to the more stable *anti* form is observed. Addition of copper powder, however, results in a complete decomposition.

Measurement of the dipole moments of several pairs of isomeric diazocyanides has confirmed the conclusions of Hantzsch that the *anti* forms are the stable isomers.¹⁰ The progress of the spontaneous isomerization of the *cis* into the *trans* forms in benzene solution was followed by means of dielectric-constant measurements. The activation energy for the conversion of *p*-bromobenzenediazocyanide was found to be 21.6 kcal., which is nearly the same as that for the conversion of *cis*- into *trans*-azobenzene, leading to the suggestion that both transformations proceed by the same mechanism.

Hantzsch¹¹ prepared *syn*- and *anti*-diazosulfonates by the action of potassium sulfite on diazonium salts. Both *syn* and *anti* forms were reduced to give the same potassium phenylhydrazine sulfonate, $\text{C}_6\text{H}_5\text{-NHNHSO}_3\text{K}$.



The action of alkali on diazonium salts converts them into *syn*- and *anti*-potassium diazotates. In the case of potassium *p*-nitrophenyl diazotate, the two forms are stable enough to isolate.¹² The *syn* isomer

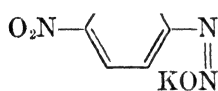


FIG. 14

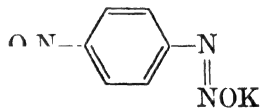
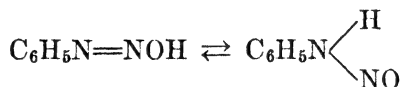


FIG. 15

(Fig. 14) forms first, but gradually changes over to the more stable *anti* isomer (Fig. 15). In the older literature, the *anti* diazotate is frequently called the isodiazotate. The existence of these isomers has also been explained on the basis of tautomerism, but this explanation has



less experimental foundation than the *syn* and *anti* type of isomerism which Hantzsch originally suggested.

¹⁰ Le Fèvre and Vine, *ibid.*, 431 (1938).

¹¹ Hantzsch, *Ber.*, **27**, 1715, 1726 (1894).

¹² Schraube and Schmidt, *Ber.*, **27**, 514 (1894).

Müller¹³ obtained isomeric forms of certain azoxy compounds (e.g., Figs. 16 and 17) which are of the *cis-trans* type. He has shown that these isomers have quite different dipole moments and concludes that the *trans* form (Fig. 17) is the one having the smaller value.

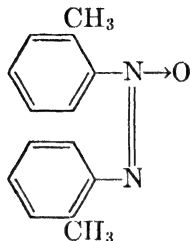


FIG. 16

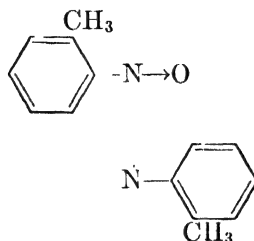


FIG. 17

Cyclic Compounds

Carbocyclic Compounds. The best experimental evidence now available indicates that the atoms in three-, four-, and five-membered rings lie in one plane and the substituents fall in two planes, one on each side of the plane of the ring (Figs. 1-3). In these molecules the cyclic

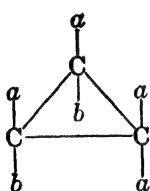


FIG. 1

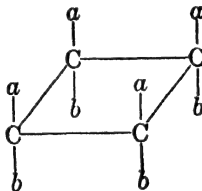


FIG. 2

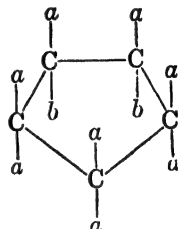


FIG. 3

structures restrict the freedom of rotation around the single bonds between the atoms in the ring, and when two or more atoms in such a ring are unsymmetrically substituted, *cis-trans* isomerism is encountered.

Six-membered rings very probably assume a strainless configuration (p. 69) and, therefore, are non-planar; yet, as far as the experimental evidence now goes, the occurrence of *cis-trans* isomerism in these rings may be considered along with that in the planar rings. Little is known experimentally concerning the possibilities for *cis-trans* isomerism with rings of more than six atoms. It seems very likely that *cis-trans* isomerism will be encountered in these molecules where two or more ring atoms are unsymmetrically substituted unless the ring is of such a large size that there is no longer any restriction to free rotation around the single bonds which hold it together.

¹³ Müller, *Ann.*, **495**, 132 (1932).

Relationship between cis-trans and Optical Isomerism in Cyclic Compounds. It should be remembered that *cis-trans* isomerism in cyclic molecules is often closely associated with optical isomerism (p. 315). For example, the cyclopropane molecule shown in Fig. 1 is a *cis* form, and it is also a *meso* form. The corresponding *trans* form (Fig. 4) is one of a racemic pair. The cyclopentane molecule shown in Fig. 3 is likewise a *cis* and *meso* form, whereas the *trans* form of this compound (Fig. 5) is one of a racemic pair.

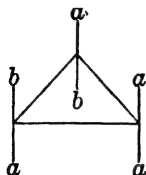


FIG. 4

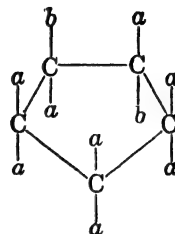


FIG. 5

In cyclic molecules there is often *cis-trans* isomerism without optical isomerism. The 1,4-disubstituted cyclohexanes (Figs. 6 and 7) and the 1,3-disubstituted cyclobutanes (Figs. 7 and 8) offer illustrations.

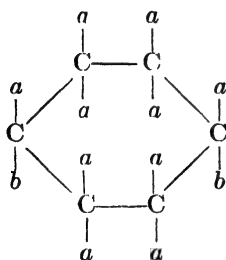


FIG. 6

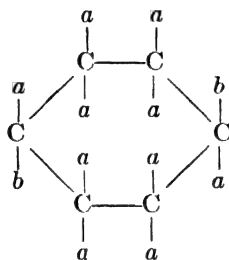


FIG. 7

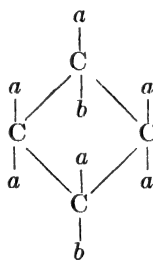


FIG. 8

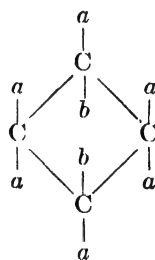


FIG. 9

Determination of Configuration. The best method of determination of the structure of *cis-trans* isomers in the cyclic series is to test the resolvability of the molecule. As indicated in the preceding section, many *cis* forms are *meso*, whereas the corresponding *trans* forms are racemic and resolvable. This method of structure proof, though limited in its application, is the most trustworthy method where it can be utilized.

Böeseken¹ devised a satisfactory method for determining the configuration of 1,2-dihydroxy compounds. A *cis*-1,2-dihydroxy compound adds boric acid to give a cyclic complex (Fig. 10) which is a much stronger

¹ Böeseken, *Rec. trav. chim.*, **40**, 553 (1921); Hermans, *Proc. Acad. Sci. Amsterdam*, **26**, 32 (1923).

acid than boric acid, whereas a *trans*-1,2-dihydroxy compound does not form such a complex.

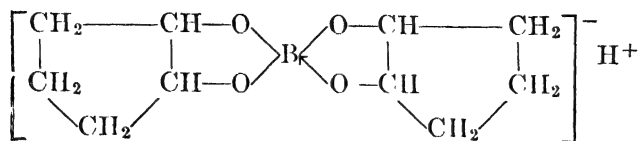


FIG. 10

Physical properties, such as melting point, solubility, and conductivity of acids, which aid in assigning configurations to *cis-trans* isomers in the olefin series, are of little use in the cyclic series because there are too many exceptions.

The following table, prepared by R. Kuhn,² shows the properties of the hexahydrophthalic acids.

| Hexahydrophthalic Acid | M. P. | Solubility in Water | K_1 |
|------------------------|-------|---------------------|----------------------|
| <i>o</i> { <i>cis</i> | 190° | Greater | 4.6×10^{-5} |
| <i>trans</i> | 215 | Less | 6.6×10^{-5} |
| <i>m</i> { <i>cis</i> | 162 | Greater | 8.0×10^{-5} |
| <i>trans</i> | 147 | Less | 4.9×10^{-5} |
| <i>p</i> { <i>cis</i> | 163 | Greater | 3.6×10^{-5} |
| <i>trans</i> | > 300 | Less | 6.6×10^{-5} |

In the cyclic molecules, as in the olefin series, it is to be expected that *cis* groups will react more readily with each other than do *trans* groups, and this aids in the determination of configuration. Thus, in the camphor series, camphoric acid (Fig. 11), which is the *cis* form, readily gives an anhydride, whereas isocamphoric acid (Fig. 12) does not give one.³

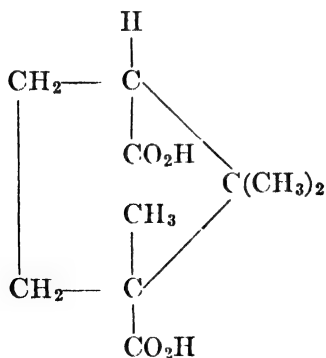


FIG. 11

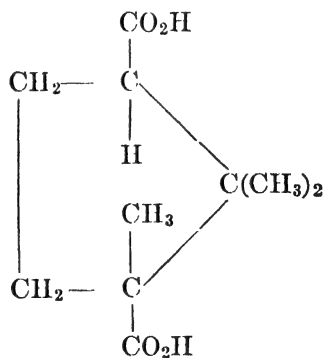


FIG. 12

² Kuhn, *Helv. Chim. Acta*, **11**, 71 (1928).

³ Aschan, *Ber.*, **27**, 2001 (1894).

Yet, *trans* dibasic acids frequently do give anhydrides, and hence the mere fact that a dibasic acid does give an anhydride is not a proof that it is a *cis* form. However, it is usually true that the *trans* anhydrides are less stable than the *cis*, and often rearrange to the *cis* forms. For example, the racemic cyclohexane-1,2-dicarboxylic acid which is *trans* (Fig. 13) gives an anhydride (Fig. 14) which, on heating, rearranges to the anhydride (Fig. 15) of the *cis* or *meso* dibasic acid (Fig. 16).⁴

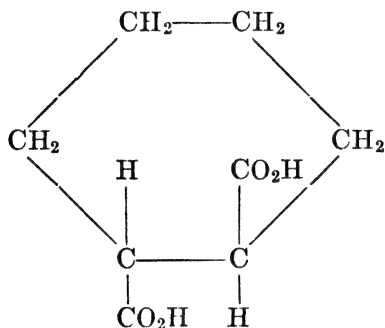


FIG. 13

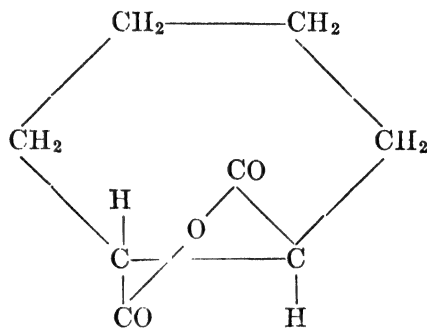


FIG. 14

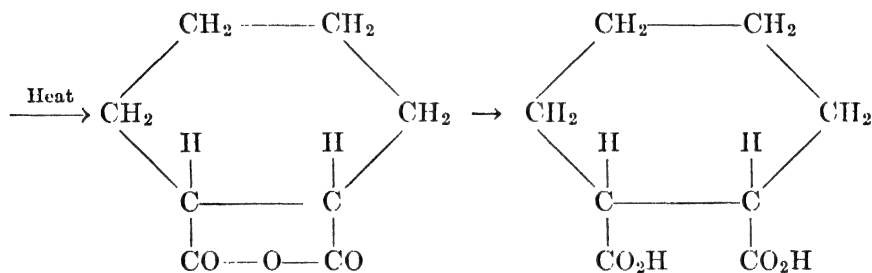


FIG. 15

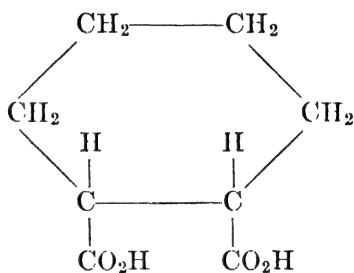


FIG. 16

Heats of combustion of the anhydrides of cyclohexane-1,2-dicarboxylic acid indicate that the *trans* anhydride is the less stable.⁵

The opening of one ring in a bicyclic molecule, as in the hydrolysis of *cis*-cyclopentene oxide (Fig. 17), would be expected to lead to a *cis* form of a monocyclic molecule. However, this does not follow, for Böeseken⁶ showed that the above oxide gives a glycol (Fig. 18) which must be the *trans* form since it is resolvable.

Wislicenus⁷ devised one certain method of determining configurations which is based on the same general principle as Körner's method of determining orientation in the benzene ring. The two forms of 2,5-

⁴ Baeyer, *Ann.*, **258**, 217 (1890).

⁵ Roth and Müller, Landolt-Börnstein, Springer, Berlin, Fifth Ed., Suppl. part 1, p. 875

⁶ Böeseken, *Rec. trav. chim.*, **39**, 183 (1920).

⁷ Wislicenus, *Ber.*, **34**, 2565 (1901).

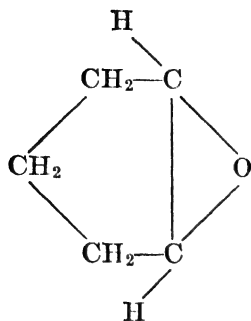


FIG. 17

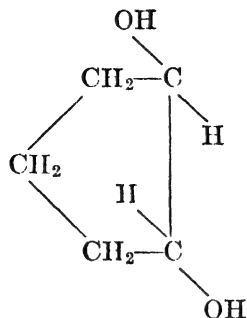


FIG. 18

dimethylcyclopentane-1,1-dicarboxylic acid (Figs. 19 and 20) can be distinguished by the number of isomeric products which are formed by the loss of one molecule of carbon dioxide from the dibasic acid. The loss of carbon dioxide from the *cis* form (Fig. 19) leads to two possible monobasic acids (Figs. 21 and 22), whereas the loss of carbon dioxide from the *trans* form (Fig. 20) leads to a single monobasic acid (Fig. 23). Wislicenus was able to assign definite configurations to the two monobasic acids (Figs. 21 and 22) by an ingenious scheme. Mild hydrolysis of the

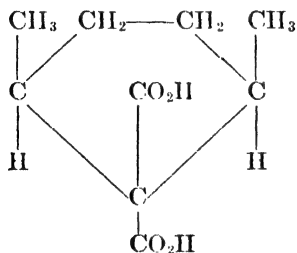


FIG. 19

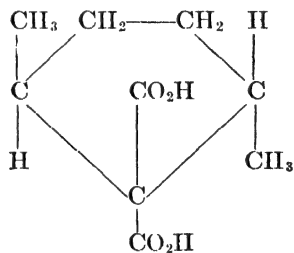


FIG. 20

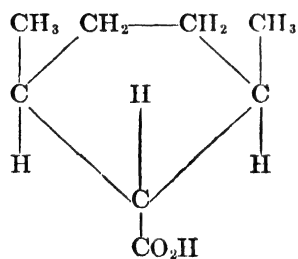


FIG. 21

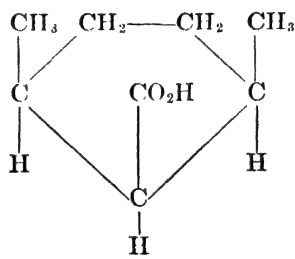


FIG. 22

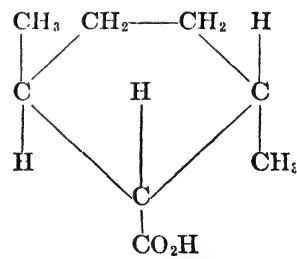


FIG. 23

diethyl ester of the dibasic acid (Fig. 19) gave an acid ester. The ester group which would hydrolyze most easily is the unhindered one which is below the plane of the ring (Fig. 19). Elimination of carbon dioxide from the resultant acid ester followed by vigorous hydrolysis of the remaining ester group gave a single monobasic acid which must have the structure shown in Fig. 22.

The use of the idea of steric hindrance has also served to distinguish between hydromellitic acid (Fig. 24) and isohydromellitic acid (Fig. 25). The latter gives a monomethyl ester when treated with methyl alcoholic

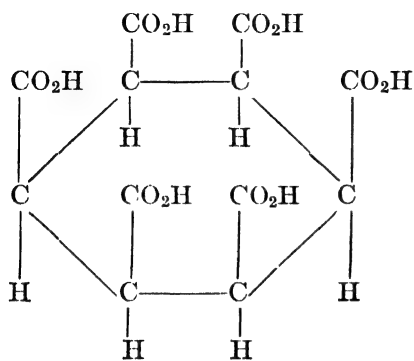


FIG. 24

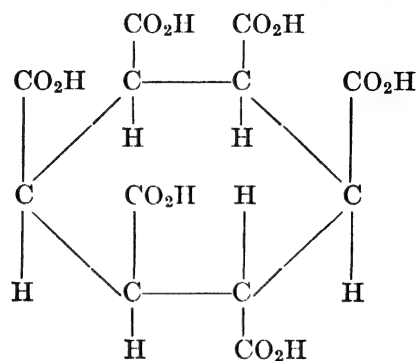


FIG. 25

hydrogen chloride, whereas the former remains unesterified.⁸ Likewise, Vavon⁹ assigned structures to certain monosubstituted cyclohexanols (Fig. 26) on the basis that the *cis* forms are more difficult to esterify, and their esters are more difficult to saponify.

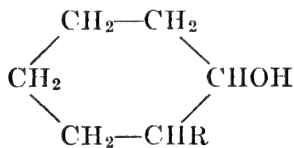


FIG. 26

Interconversion of Isomers. Interconversion of *cis-trans* isomers in the cyclic series takes place readily only when there is a chance for tautomerism. Examples are menthone¹⁰ (Fig. 27), the hexahydrophthalic acids, and camphoric acid¹¹ (Fig. 28). The reagents which

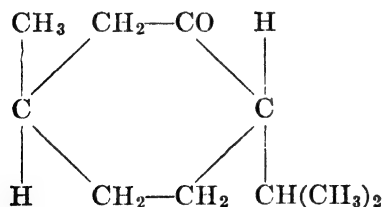


FIG. 27

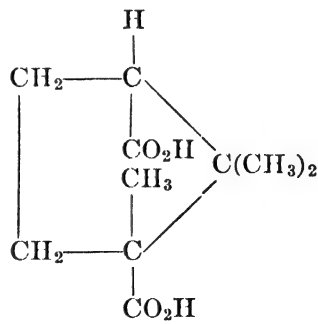


FIG. 28

⁸ van Loon, *Ber.*, **28**, 1270 (1895).

⁹ Vavon, *Bull. soc. chim.*, [4] **39**, 666 (1926); **43**, 667 (1928).

¹⁰ Beckmann, *Ann.*, **250**, 334 (1889).

¹¹ Aschan, *Ann.*, **316**, 217 (1901); **387**, 16 (1912).

cause the conversion of one form to another are those which also favor enolization.

Heterocyclic Compounds. The introduction of a hetero atom such as oxygen, nitrogen, or sulfur in the cyclic system does not change the real ring structure, since these atoms are tetrahedral. The cyclic acetals in the sugar series are well-known examples of the heterocyclic compounds with oxygen in the ring. Cornubert and Robinet ¹² have recently isolated the two forms of α, α' -diphenyltetrahydro- γ -pyrone (Fig. 29). The chapter on alkaloids (p. 1166) furnishes illustrations of *cis-trans* isomerism involving nitrogen rings.

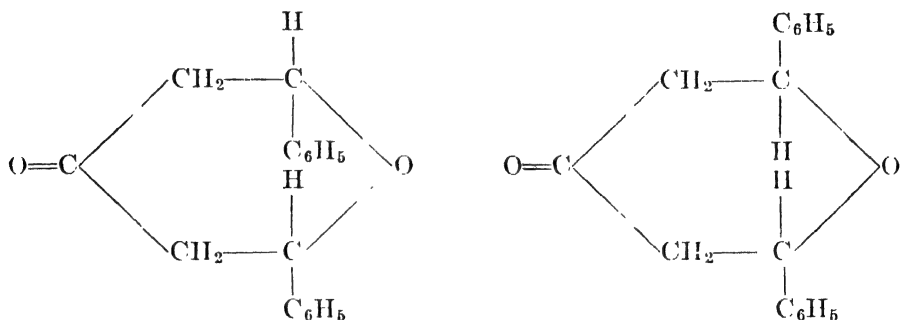


FIG. 29

Some interesting examples of *cis-trans* isomerism in rings containing sulfur oxidized to the sulfoxide stage have been investigated. Bennett and Waddington ¹³ separated several pairs of the sulfoxides of penthianols (Fig. 30). Bell and Bennett ¹⁴ isolated the *cis* and *trans* forms of

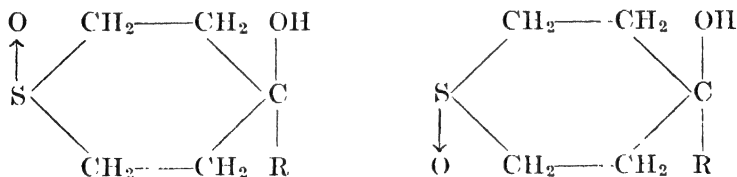


FIG. 30

the disulfoxide of 1,4-dithian (Fig. 31). The same authors ¹⁵ isolated the

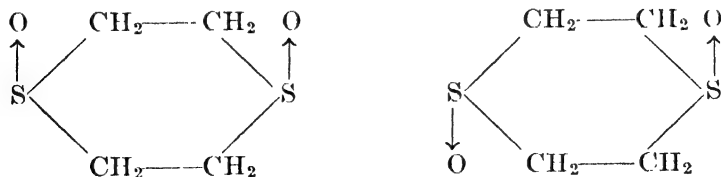


FIG. 31

¹² Cornubert and Robinet, *Bull. soc. chim.*, [5] 1, 90 (1934).

¹³ Bennett and Waddington, *J. Chem. Soc.*, 2832 (1929).

¹⁴ Bell and Bennett, *ibid.*, 1798 (1927).

¹⁵ Bell and Bennett, *ibid.*, 15 (1929).

various *cis-trans* isomers of the di- and trisulfoxides from trithian (Fig. 32).

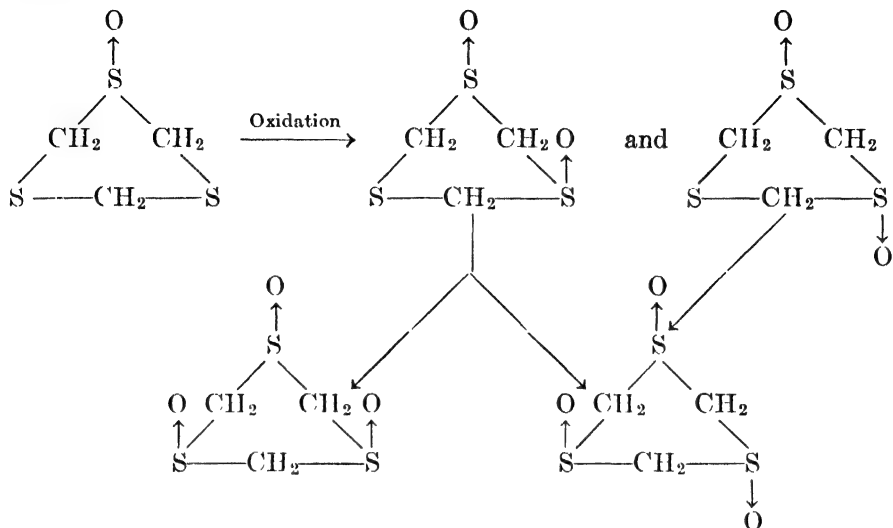


FIG. 32

Condensed Ring Systems. *cis-trans* Isomers exist in certain condensed ring systems, but not in others. If the rings are fused in the 1,2-positions, two isomers may be obtained when both rings contain six atoms, both rings contain five atoms, or one ring contains six atoms and one contains five atoms. Hückel¹⁶ isolated the *cis* (Fig. 33) and *trans* (Fig. 34) forms of decahydronaphthalene. Helfer¹⁷ obtained two forms

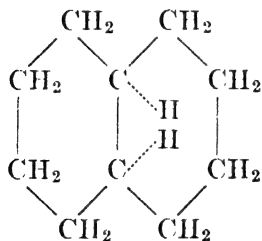


FIG. 33

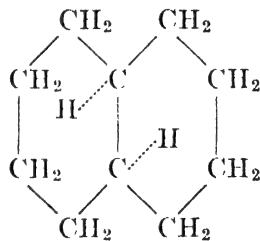


FIG. 34

of decahydroisoquinoline (Fig. 35), and Böeseken and his co-workers¹⁸ prepared the *cis* and *trans* forms of naphthodioxane (Fig. 36), thus showing that condensed heterocyclic systems behave like the homocyclic

¹⁶ Hückel, *Ann.*, **441**, 1 (1925); **451**, 109 (1926).

¹⁷ Helfer, *Helv. Chim. Acta*, **6**, 795 (1923); **9**, 814 (1926).

¹⁸ Böeseken, Tellegen, and Henriquez, *Rec. trav. chim.*, **50**, 909 (1931).

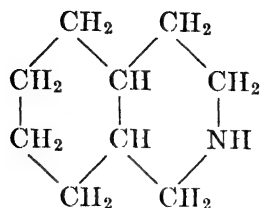


FIG. 35

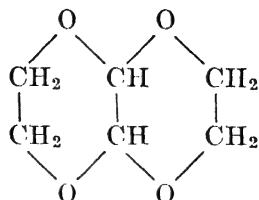


FIG. 36

systems. Hückel and Friedrich¹⁹ showed that hexahydrohydrindanone (Fig. 37) occurs in two forms which are *cis* and *trans* isomers.

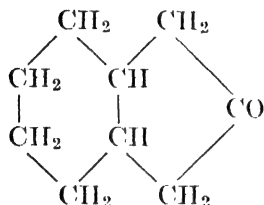


FIG. 37

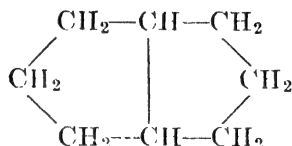


FIG. 38

The existence of two forms of 3,3,0-bicyclooctane²⁰ (Fig. 38) is evidence for the occurrence of *cis-trans* isomers in fused five-membered rings of the 1,2 type.

Cyclohexene oxide²¹ (Fig. 39) has been found in only one form, thus indicating that a three-membered ring fused to a six-membered ring in

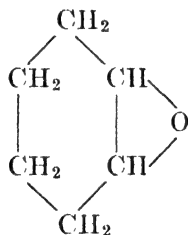


FIG. 39

the 1,2-position is too highly strained to exist in a *trans* modification. For the same reasons, it seems unlikely that the *trans* isomers will be encountered in any 1,2 condensed ring system which has as one of its members a ring of less than five atoms.

A considerable number of compounds is known in which two six-membered rings are fused through the 1,3- and the 1,4-positions. The

¹⁹ Hückel and Friedrich, *Ann.*, **451**, 132 (1926).

²⁰ Linstead and Meade, *J. Chem. Soc.*, 935 (1934); Barrett and Linstead, *ibid.*, 436 (1935).

²¹ Bartlett, *J. Am. Chem. Soc.*, **57**, 224 (1935).

trans forms are highly strained configurations, and the experimental evidence points to the existence of only the *cis* isomers. Examples of these types of condensed nuclei are 3,3,1-bicyclononane²² (Fig. 40), camphane²³ (Fig. 41), and 2,2,2-bicycloöctane²⁴ (Fig. 42).

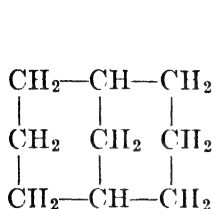


FIG. 40

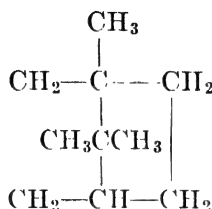


FIG. 41

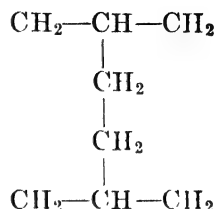


FIG. 42

The condensed ring systems are of considerable importance in connection with the chemistry of the alkaloids (p. 1166), terpenes (p. 70), sterols (p. 1379), and related compounds.

Terphenyl Derivatives

In 1929 Stanley and Adams¹ pointed out that terphenyl derivatives substituted in the positions *ortho* to the pivot bond joining the phenyl groups and unsymmetrically substituted in the terminal phenyl groups could exist in *cis* and *trans* forms. Several derivatives of this type have been prepared, and most of them are also isomers of the racemic and *meso* types as well as of the *cis-trans* type. Since these have already been described in the section on optical isomerism (p. 370), only the *cis-trans* isomers which do not show optical isomerism will be considered here.

If the central benzene ring in the terphenyl derivative is substituted with four like groups, the resulting terphenyls are not asymmetric, but *cis-trans* isomerism is possible (Figs. 1 and 2).

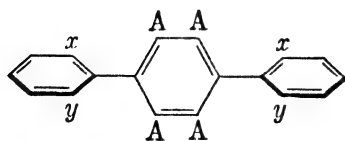


FIG. 1

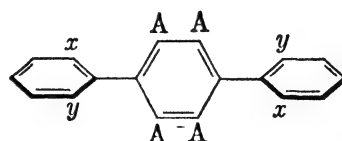


FIG. 2

²² Meerwein and Schürmann, *Ann.*, **398**, 196 (1913); *J. prakt. Chem.*, **104**, 161 (1922).

²³ Hückel, *Ann.*, **455**, 123 (1927).

²⁴ Alder and co-workers, *Ann.*, **514**, 1 (1934); Kasansky and Plate, *Ber.*, **68**, 1259 (1935).

¹ Stanley and Adams, *Rec. trav. chim.*, **48**, 1035 (1929).

Shildneck and Adams ² prepared the *cis* and *trans* isomers of 2,5-di-(3-bromo-2,4,6-trimethylphenyl)-1,3,4,6-tetrahydroxybenzene (Fig. 3) and of some of their tetraacyl derivatives (Fig. 4).

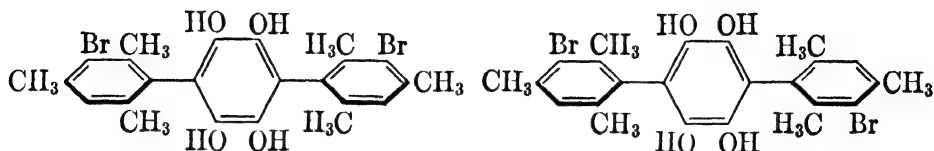


FIG. 3

These pairs of compounds were remarkably stable to attempts at direct conversion of one form to the other. Naturally, the same condi-

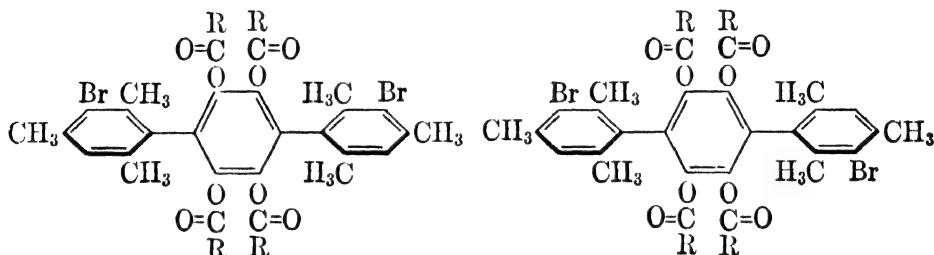


FIG. 4

tions which favor racemization of optically active biphenyl and terphenyl derivatives will favor interconversion of these *cis* and *trans* forms. There is no general method of determining the configuration of terphenyls which are not also optically active. When optical activity is possible, the determination of *cis* and *trans* configurations can be made by relating the isomers to *meso* and racemic forms.

This type of *cis-trans* isomerism which is dependent on restricted rotation around a single bond has been predicted for quaterphenyls ³ and will undoubtedly be discovered in other series as well.

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² Shildneck and Adams, *J. Am. Chem. Soc.*, **53**, 2203 (1931).

³ Adams and Yuan, *Chem. Rev.*, **12**, 261 (1933).

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The authors are deeply indebted to many chemists for assistance in the preparation and revision of this chapter. Especial thanks are due to Dr. J. K. Senior of the University of Chicago, and to their colleagues, Drs. H. R. Snyder, C. C. Price, and F. T. Wall at the University of Illinois. Much assistance was given by Drs. G. A. Nesty, P. S. Pinkney, E. J. Dobratz, and J. O. Corner in searching the literature and in organizing the material. Many teachers and students have contributed corrections and suggestions. To all these the authors express their thanks and cordially invite constructive comments for future revisions.

CHAPTER 5

ORGANOMETALLIC COMPOUNDS

HENRY GILMAN
Iowa State College

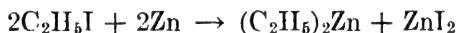
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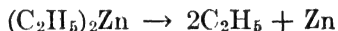
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HISTORICAL

Frankland,¹ in 1849, was the first to isolate an organometallic compound and then establish its constitution. He set out to prepare the free ethyl radical, using zinc to remove iodine from ethyl iodide, and obtained instead diethylzinc.



Then, in a series of classical investigations with inflammable and poisonous compounds, he extended his studies to other metals and soon laid the groundwork of much of our present knowledge of organometallic chemistry. Although Frankland did not realize his primary objective of preparing alkyl radicals, it is significant that his organometallic compounds provided the essential means, long years later, for the preparation of free alkyl radicals by pyrolysis.



In free radical chemistry, organometallic compounds not only are useful for the preparation of free organic radicals and the identification of free radicals (by combinations with metals to give organometallic derivatives), but also their use provides a satisfactory means for establishing, uniquely in many cases, the existence of some elements in so-called abnormally valenced states like tetravalent chromium in R_4Cr .

Frankland, before going deeply in his work, said that he "became impressed with the fixity in the maximum combining power or capacity of saturation in the metallic elements which had not before been suspected." The strenuously advocated case by Kekulé and others for a

¹ Frankland, *Ann.*, **71**, 213 (1849).

fixity in valence found support, therefore, in the early work with organometallic compounds. It is interesting to note, then, how the whole picture of valence, as it concerned organometallic compounds, changed over the years: at first, organometallic chemistry did much to sustain the concept of fixity in valence; later, it provided a very useful tool to establish the wide variability in valence for certain elements.

DEFINITION

Broadly speaking, organometallic compounds are compounds which have a direct union of carbon with a metal. There is no agreement on the definition of a metal. To some, the elements are very largely metallic and to such an extent that, of the 92 known elements, 68, or 74 per cent of the total, are metals; 11 of the remainder or 12 per cent of all the elements have some of the properties of metals (B, C, Si, P, As, Sb, Sc, Te, Po, I, and Element 85); and only 13 elements are non-metals (H, N, O, S, F, Cl, Br, He, Ne, A, Kr, Xe, Rn).² The organic chemist would prefer to delimit the "somewhat metallic" elements to exclude at least phosphorus, selenium, and iodine; and he would wisely elect to consider carbon in organic compounds as a non-metal, if only to avoid classifying practically all organic compounds as organometallic compounds.

There are numerous types of organometallic compounds. Those having but one metal may contain one or more R groups and one or more X groups, depending on the valence of the metal and the stabilities of the organometallic compounds: $\text{C}_2\text{H}_5\text{Na}$, $(\text{CH}_3)_3\text{Al}$, $\text{CH}_3\text{HgC}_6\text{H}_5$, $\text{C}_6\text{H}_5\text{BeCl}$, $(\text{C}_6\text{H}_{11})_2\text{PbBr}_2$, CH_3SnCl_3 . The R group can be aliphatic, alicyclic, or aromatic, and although it may have a wide variety of substituents it obviously cannot contain a substituent which can react with the selected organometallic linkage. For example, no compound like $\text{H}-\text{C}-\text{C}_6\text{H}_4\text{MgBr}$ is known because of the prompt and vigorous



reaction of an RMgX compound with an aldehyde. X may be halogen, or almost any acid radical, hydrogen, hydroxyl, amino, or other group depending on the organometallic type; but the X group cannot be one which reacts with the selected organometallic type, and this would rule out the possibility of $\text{C}_2\text{H}_5\text{CaOH}$ inasmuch as organocalcium compounds react vigorously with the hydroxyl group. The metal might be an integral part of a cyclic structure like pentamethylenemercury, $(\text{CH}_2)_5\text{Hg}$; or it may be attached to a methylene group in a simple

² Fernelius and Roby, *J. Chem. Education*, **12**, 53 (1935).

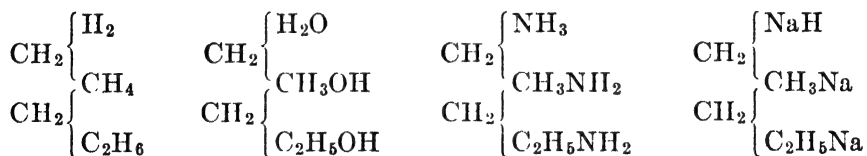
type like methylene-aluminum iodide, $\text{CH}_2=\text{AlI}$. Where two or more atoms of a metal are present, we may have the same metal as

in dodecamethylstannopentane, $(\text{CH}_3)_3\text{Sn}-\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{Sn}}}-\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{Sn}}}-\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{Sn}}}-\text{Sn}(\text{CH}_3)_3$, and

diiodozincmethane, $\text{CH}_2(\text{ZnI})_2$; or unlike metals as in 1-trimethylstannyl - 5 - trimethylplumbylpentane, $(\text{CH}_3)_3\text{SnCH}_2(\text{CH}_2)_3\text{CH}_2\text{Pb}(\text{CH}_3)_3$.

The two main classes of organometallic compounds are commonly known as "simple" and "mixed." By a simple organometallic compound is understood one which has only R groups attached to the metal (M) as R_4M , whereas a mixed organometallic compound has both R and X groups attached to the metal, as R_2MX . The simple types may be further divided into symmetrical ($\text{C}_2\text{H}_5\text{HgC}_2\text{H}_5$) and unsymmetrical ($\text{C}_2\text{H}_5\text{HgC}_4\text{H}_9$) groups.

Strictly speaking, carbides are organometallic compounds, and although some of them have general characteristics that warrant their inclusion as organometallics it would seem desirable in the space allotted to give them no more than cursory consideration. Also, metallic cyanides and metallic carbonyls are not to be considered here, partly because of some uncertainties concerning their structures but more particularly because they do not appear to have what might be termed the essential characteristics of organometallic compounds. In view of such arbitrary limitations it may appear surprising to suggest the inclusion of compounds that have no carbon and so are not organic in a strict sense. However, a case of sorts can be made for the metallic hydrides. Several homologous series have as theoretical first members a simple inorganic substance



whose general properties warrant consideration with the organic members of the series. On such a basis, the first member of each series of simple organometallic compounds is a metallic hydride. Actually, some metallic hydrides do exhibit properties highly reminiscent of the organometallic compounds containing that metal.³

It should be stated at this place that organometallic compounds

³ Kraus, *ibid.*, 6, 1478 (1929).

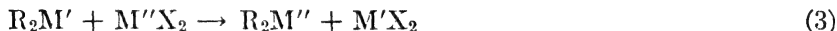
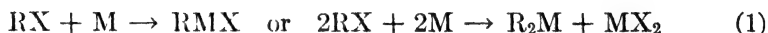
have not been prepared from all metals. There are some who believe that certain metals cannot form organometallic compounds. It is probable, however, that all metals will form organometallic compounds.

OCCURRENCE

The only reported occurrences in nature of compounds which might be considered to be organometallic are those of moissanite, SiC, and of cohenite (FeCoNi)₃C. Both compounds have been found in meteorites. The great stability of certain types of organometallic compounds warrants the prediction that others may be found.

PREPARATION

There are many procedures, general and specific, for the preparation of organometallic compounds. Some of these will be considered subsequently, but at this time it would seem desirable to mention three syntheses of wide application.



Basically, therefore, organometallic compounds derive from interaction of an RX compound with a metal or its alloy or amalgam. This applies particularly to the preparation of organozinc, -magnesium, and -lithium compounds, which are among the most effective types for the transformations illustrated in reactions 2 and 3. The historically important organozinc compounds have been largely superseded for synthetic purposes by the magnesium and lithium compounds which are less inflammable, less toxic, and more conveniently manipulated. Although organozinc and -mercury compounds still find use for the synthesis of other organometallic compounds it is significant that many zinc and mercury compounds are best prepared from the corresponding organo-magnesium and -lithium compounds.

In reaction 2, M'' is generally of a higher potential or above M' in the electromotive series; but in reaction 3, the reverse relationship generally holds, and M'' is below M' in the electromotive series. It should be stated, however, that the reactions are not typically electrochemical in kind and that they are often reversible. As specific illustrations we have: the Grignard reagent formed in accordance with reaction 1; organolithium compounds formed from metallic lithium and the RMgX compound in accordance with reaction 2; and organo-

aluminum compounds formed from aluminum chloride and the Grignard reagent in accordance with reaction 3. In general, a more reactive organometallic compound is formed from a less reactive compound in reaction 2; and a less reactive organometallic compound is formed from a more reactive compound in 3. These generalizations apply to all organometallic compounds so that one might expect to use any RM compound for the synthesis of all other organometallic compounds. Something approaching this has been realized with the Grignard reagent, which has been used, at one time or another, for the preparation of practically all other organometallic compounds, the more reactive ones being prepared from RMgX and a metal, and the less reactive ones from RMgX and a metallic halide.

PROPERTIES

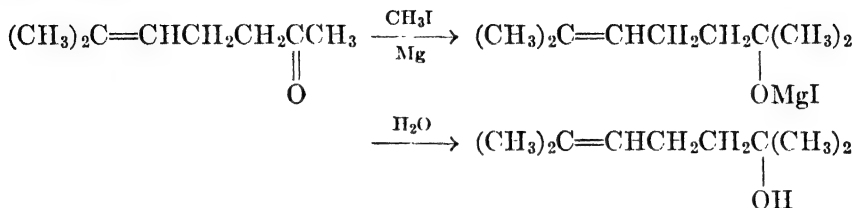
The physical, chemical, and physiological properties of the numerous different types of organometallic compounds vary greatly. However, certain classes of RM compounds can be grouped conveniently. A simple and effective system of classification is by groups in the periodic table, and the organometallic compounds will be considered here in the order of such periodic groups. Fortunately, there are available two reactions which can be used further to simplify classification into the following three divisions on the basis of relative reactivities: (1) the highly reactive compounds; (2) the moderately reactive compounds; and (3) the relatively unreactive compounds. The two reactions are addition to an olefinic linkage and addition to a carbonyl group. The highly reactive compounds add to both the olefinic linkage and the carbonyl group; the moderately reactive compounds add only to the carbonyl group; the relatively unreactive compounds add neither to the olefinic linkage nor to the carbonyl group in reasonable time.

In order to gain a broad survey of the whole domain of organometallic compounds there appear to be certain advantages to a prior consideration of a moderately reactive type, for not only do all moderately reactive compounds show the same general reactions, at different rates, but the highly reactive compounds also show such reactions in addition to the special reaction mentioned with the olefinic linkage.

A moderately reactive RM type is the Grignard reagent. RMgX compounds are, at this time, the most important group of organometallic compounds, and a general knowledge of their properties should provide a useful basis for orienting and correlating the other types.

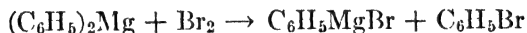
GRIGNARD REAGENTS

Historical. The first application of magnesium in synthetic organic chemistry was made by Barbier,⁴ who in 1899 obtained dimethylheptenol from interaction of a mixture of methylheptenone, methyl iodide, and magnesium in ether.

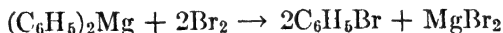


Then, in 1900, his student, Grignard,⁵ resolved this typical synthesis into two reactions: first, preparing the RMgX compound in ether solution; and then treating the organomagnesium halide with a reactant. Grignard promptly realized the great possibilities of the reagent which later came to bear his name, and in a series of vigorously prosecuted studies he laid the foundations for much of our present knowledge of the reagent and its reactions. For his elegant work which provided organic chemists a most useful tool for syntheses he was awarded a Nobel prize in 1912.

Long years before Grignard made his discovery, Hallwachs and Schafarik⁶ prepared an organomagnesium compound by heating ethyl iodide with magnesium. On the basis of their examination they concluded that their product contained traces of diethylmagnesium. Later, Fleck^{7a} purposefully set out to prepare phenylmagnesium bromide (by the slow addition of bromine to diphenylmagnesium in anhydrous ether) in accordance with the following reaction written by him.



However, because he obtained only bromobenzene and magnesium bromide he pictured the course of reaction as follows:



and concluded that a stable compound corresponding with the formula $\text{C}_6\text{H}_5\text{MgBr}$ was not formed. Subsequently, it was shown by others^{7b}

⁴ Barbier, *Compt. rend.*, **128**, 110 (1899).

⁵ Grignard, *ibid.*, **130**, 1322 (1900).

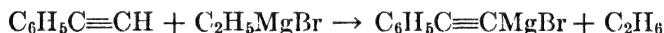
⁶ Hallwachs and Schafarik, *Ann.*, **109**, 206 (1859).

⁷ (a) Fleck, *Ann.*, **276**, 129 (1893). (b) Gilman and Brown, *J. Am. Chem. Soc.*, **52**, 1181 (1930).

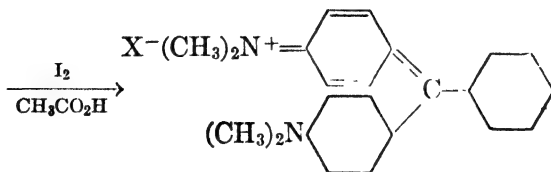
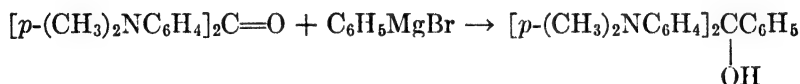
that phenylmagnesium bromide was initially formed and that the unfortunate addition of bromine in excess destroyed the first organomagnesium halide prepared in ether.

Preparation. The Grignard reagent is readily and conveniently prepared in dry ether. Some RX compounds react slowly, but by appropriate catalytic devices it is possible to initiate and accelerate the reaction. The yields are highly satisfactory, and the more frequently used Grignard reagents are obtainable in about 90–95 per cent yield. The commonly used solvent, diethyl ether, may be replaced by other ethers or tertiary amines. The preparation can also be effected without a solvent. Fortunately, it is not necessary to isolate the reagent, and the manipulation is simplified by preparing the solution in a suitable container and then adding the reactant, a procedure which reminds one of diazonium reactions.

Occasionally the reagent is prepared indirectly by interaction of a Grignard reagent with an active or acidic hydrogen attached to carbon.



Analysis. A sensitive, qualitative color test^{8a} for the Grignard reagent and other moderately reactive as well as for the highly reactive organometallic compounds is readily carried out by means of Michler's ketone (*p,p'*-tetramethyldiaminobenzophenone). One-half to one cubic centimeter of the organometallic solution is added to an equal volume of a 1 per cent solution of Michler's ketone in dry benzene; the reaction product is then hydrolyzed by the slow addition of 1 cc. of water; and, finally, the addition of several drops of a 0.2 per cent solution of iodine in glacial acetic acid develops a characteristic greenish-blue color. With phenylmagnesium bromide, as an illustration, the product is malachite green.

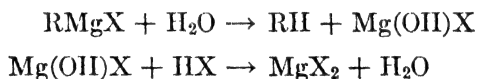


With radicals other than phenyl attached to the metal, the color is due to a related di- or triphenylmethane dye.

^{8(a)} Gilman and Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925). (b) Gilman and Swiss *ibid.*, **62**, 1847 (1940). (c) Gilman and Yablunky, *ibid.*, **63**, 839 (1941).

Inasmuch as the color test is directly associated with a compound having a carbon-metal linkage and not with compounds having a metal attached to an element other than carbon, the test is useful for determining when a reaction is complete, for if the organometallic compound be not used in excess the product in the reaction mixture will not have a carbon-metal linkage and hence will not give a color test. Some acid chlorides and pyrrole interfere with the Michler's ketone test or color test I. There are two other color tests. One of these,^{8b} color test II (p. 525), differentiates between Grignard reagents and organolithium compounds; the other,^{8c} color test III (p. 564), is given by reactive arylmetallic compounds, but not by alkylmetallic compounds.

A simple procedure for the quantitative estimation of reactive and moderately reactive organometallic compounds is to hydrolyze an aliquot and titrate the basic compound formed with a standard acid.^{9a}



Physical Properties. The RMgX compounds are colorless solids which do not melt but decompose at elevated temperatures, first undergoing, in all probability, the following transformation, which may be general for all mixed organometallic compounds:



It is possible to ether-distil alkylmagnesium halides, but inasmuch as the R_2Mg and the MgX_2 compounds can also be ether-distilled separately there is no definite evidence that the RMgX found in the distillate comes over as such.^{9b}

The dialkylmagnesium compounds are colorless crystals which can be sublimed under greatly reduced pressures, dimethylmagnesium being most volatile. Under such conditions it is possible to obtain pure dimethylmagnesium from methylmagnesium chloride.^{9c} The thermal decomposition of methylmagnesium iodide^{10a} occurs at 240° .

Chemical Properties. Inasmuch as the following equilibrium is characteristic of Grignard reagents, it is clear that such reagents are really mixtures and that Grignard reactions are reactions of RMgX , R_2Mg , and MgX_2 compounds.

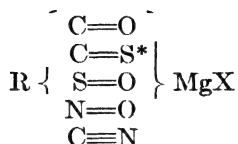


⁹ (a) Gilman, Wilkinson, Fishel, and Meyers, *ibid.*, **45**, 150 (1923); Houben, Boedler, and Fischer, *Ber.*, **69**, 1766 (1936). (b) Gilman and Brown, *J. Am. Chem. Soc.*, **52**, 4480 (1930). (c) Gilman and Brown, *Rec. trav. chim.*, **48**, 1133 (1929).

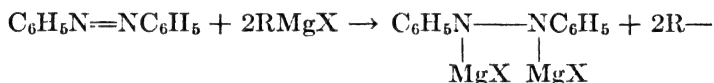
¹⁰ (a) Jolibois, *Compt. rend.*, **156**, 712 (1913). (b) Coleman, Gilman, Adams, and Pratt, *J. Org. Chem.*, **3**, 99 (1938).

However, RMgX and R_2Mg compounds show the same reactions, almost without exception, and differ essentially only in rates of reaction.

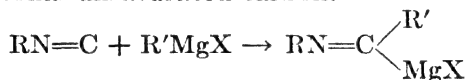
The Grignard reagents almost invariably react as R and MgX units. In addition reactions to an unsaturated linkage, the R attaches itself to the relatively less acidic element and the MgX to the relatively more acidic element.



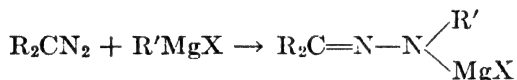
When the unsaturated linkage is made up of the same elements there are only two important types to consider. One of these is the olefinic or acetylenic linkage to which Grignard reagents do not add, or do not add at an appreciable rate. The other is the azo linkage, and here two MgX groups add, the R groups then undergoing coupling to $\text{R}-\text{R}$ compounds and disproportionation to $\text{R}(+\text{H})$ and $\text{R}(-\text{H})$ compounds (see p. 511 for a different course of reaction between azobenzene and more reactive RM compounds).



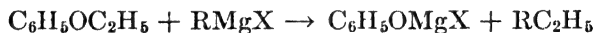
With compounds like isocyanides, the Grignard reagent adds to some extent to the terminal unsaturated carbon.



A related reaction occurs with some aliphatic diazo compounds.^{10b}



In reactions not involving addition to unsaturated linkages the same generalizations hold. That is, the R attaches itself to the relatively less acidic element and the MgX to the relatively more acidic element.



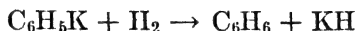
That portion of the R groups which does not combine with an element in such cleavage and related reactions couples or disproportionates.

Cleavage by Hydrogen, Active Hydrogen Compounds, and Halogens. Grignard reagents can be cleaved by hydrogen under standard hydrogenation procedures.

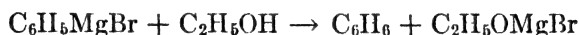


* See, Schönberg, *Ann.*, **454**, 37 (1927) for the formation of cyclic sulfides from thioketones and the Grignard reagent. Also, see p. 505 of this chapter for the reaction with both thiocyanates and with carbon disulfide.

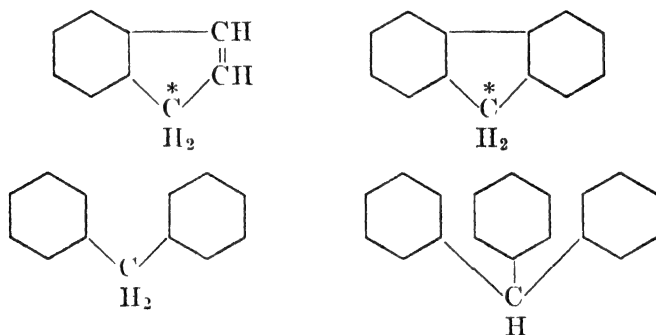
This reaction is shown by other organometallic compounds and proceeds most readily with the most reactive RM types.^{11a} Actually, phenylpotassium, for example, undergoes reaction by merely bubbling hydrogen into a petroleum ether suspension at room temperature, atmospheric pressure, and without a catalyst.^{11b}



Compounds which contain hydrogen attached to any element but carbon (and in some special cases when attached to carbon) cleave Grignard reagents in such a manner that the R group of RMgX combines with the active hydrogen.



The noteworthy types which contain an active hydrogen attached to carbon are the true acetylenes (having the $\text{—C}\equiv\text{CH}$ linkage), and the indene and fluorene types which have hydrogen attached to a carbon (indicated by an asterisk) holding two strongly negative groups.

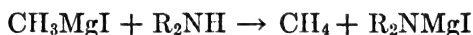


Diphenylmethane, having a carbon attached to two phenyl groups which are not bridged, has no active hydrogen as far as the Grignard reagent is concerned, but the hydrogens attached to the lateral carbon in diphenylmethane are acidic to other, more reactive organometallic compounds. The lateral hydrogen in triphenylmethane appears to be very weakly acidic, as judged by its slow replacement by —MgX when treated with a Grignard reagent.

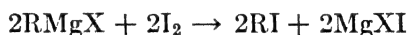
The vigorous destruction of Grignard reagents by active hydrogen attached to elements other than carbon emphasizes the necessity of excluding moisture from reagents and apparatus. The cleavage of RMgX compounds by active hydrogens can, however, be a most useful analytical reaction for two purposes. First, the concentration of low-

¹¹ (a) Zartman and Adkins, *J. Am. Chem. Soc.*, **54**, 3398 (1932); Burdick and Adkins *ibid.*, **56**, 438 (1934). (b) Gilman, Jacoby, and Ludeman, *ibid.*, **60**, 2336 (1938).

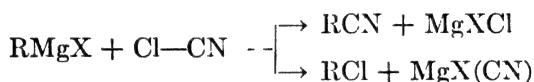
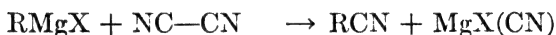
molecular-weight Grignard solutions can be determined with precision by adding an excess of water and measuring the volume of gas evolved. Also, of course, the acid-titration method of quantitative analysis of RMgX compounds depends on prior cleavage or hydrolysis. Second, the presence of active hydrogen and the number of active hydrogens in a molecule is readily determined by the widely used Tschugaeff-Zerewitinoff¹² analysis which consists essentially in adding an excess of methylmagnesium iodide to a sample of the compound to be analyzed and measuring the volume of methane evolved.



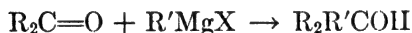
Halogens cleave RMgX compounds as follows:



The 2MgXI probably disproportionates to $\text{MgX}_2 + \text{MgI}_2$. The reaction with iodine, in particular, goes quite smoothly, and has been recommended for the quantitative analysis of Grignard reagents. However, it is less accurate and not so widely applicable as the acid-titration method of analysis.¹³ As might have been expected, cyanogen and the halogen-cyanogens behave in a similar manner, but the unsymmetrical halogen-cyanogens can cleave RMgX compounds in two ways.



Addition to Unsaturated Linkages (p. 646). The most widely used synthetic reaction of Grignard reagents involves 1,2-addition to an unsymmetrical double or triple bond. With a simple carbonyl group, alcohols are formed: formaldehyde gives a primary alcohol; other aldehydes a secondary alcohol; and ketones a tertiary alcohol.



The color test I with Michler's ketone depends on the intermediate formation of a tertiary alcohol.

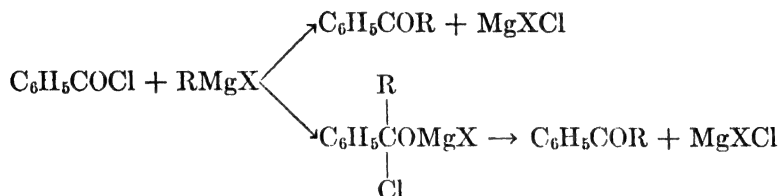
Esters (other than those of formic acid, which yield secondary alcohols) also give tertiary alcohols, but sometimes it is possible to arrest the reaction partly at the ketone stage.

¹² Zerewitinoff, *Ber.*, **40**, 2023 (1907). See, also, Tschugaeff, *Ber.*, **35**, 3912 (1902); Hibbert and Sudborough, *J. Chem. Soc.*, **85**, 933 (1904); and, particularly, Kohler, Stone, and Fuson, *J. Am. Chem. Soc.*, **49**, 3181 (1927).

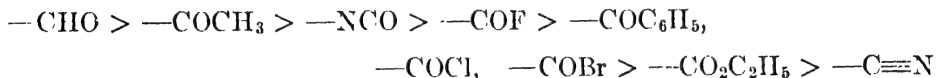
¹³ Job and Reich, *Bull. soc. chim.*, **33**, 1414 (1923); Gilman and Meyers, *Rec. trav. chim.*, **45**, 314 (1926).

In general, acids and their common derivatives like acid anhydrides, salts, acid amides, and acid halides give ketones and tertiary alcohols. The reaction with acid halides is of more than ordinary interest because of its bearing on the mechanism of reaction of Grignard reagents with acid derivatives and because acid chlorides react with a large variety of organometallic types.

In ketone formation from acid chlorides either direct replacement of chlorine by R or prior addition to the carbonyl linkage is possible.



Although there is no definite answer to the question at present, it appears on the basis of studies by Entemann and Johnson¹⁴ that reaction takes place first by addition to the carbonyl group. These authors carried out a series of competitive reactions in which one equivalent of phenylmagnesium bromide was added to a solution containing one equivalent of each of two reactants. An examination of the products revealed the extent of each reaction. For example, from a reaction between phenylmagnesium bromide and a mixture of benzophenone and benzonitrile there was recovered 98 per cent of benzonitrile and no benzophenone. Accordingly, the carbonyl group in benzophenone is much more reactive than the nitrile group in benzonitrile. On this basis the relative reactivities of some functional groups are:



If the reaction between acid halides and the Grignard reagent proceeded by direct replacement, one would expect the acid fluoride to be the least reactive of the three acid halides, for studies of other halides show rather consistently that the order of decreasing reactivity of halogens in carbon-halogen linkages is: C-Br, C-Cl, C-F. However, because the acid fluoride was actually found to be the most reactive acid halide it appears reasonable to conclude that the mechanism does not involve a metathetical reaction, but addition to the carbonyl group.

Prior addition to the carbonyl linkage of acid halides may not be true of all RM compounds. For example, some of the unreactive

¹⁴ Entemann and Johnson, *J. Am. Chem. Soc.*, **55**, 2900 (1933).

organometallic compounds will react readily with acid chlorides to give ketones, but react extremely slowly or not at all with an aldehyde like benzaldehyde. In any event there appears to be another series of relative reactivities of acid halides with the less reactive RM compounds. This finds support in the reaction between benzoyl halides and di-*p*-tolylmercury.



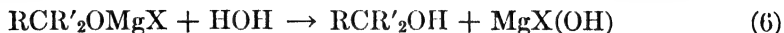
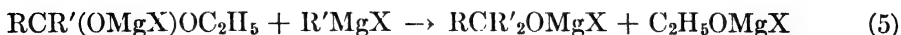
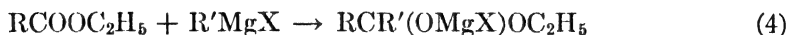
Under comparable conditions, the yield of phenyl *p*-tolyl ketone progressively decreases in the order: —COI, —COBr, —COCl, —COF. Likewise, the yield of benzophenone from phenylzinc chloride and those of the benzoyl halides examined decreases in the order: —COI, —COBr, —COCl. Even with a moderately reactive type like organoaluminum compounds, benzoyl iodide is slightly more reactive than benzoyl chloride.

This does not necessarily exclude the possibility of prior addition to the carbonyl group, in acid halides, which may have been activated by halogen. The highly reactive carbonyl group in ketene adds phenylmercuric bromide to give acetophenone¹⁵ (p. 550). Finally, even though addition does not occur at the carbonyl group, the initial coordination complex may involve the carbonyl group.

An unusually comprehensive series of studies has been carried out by Whitmore and co-workers^{16a} on the types of reaction, particularly reduction, between branched-chain acid halides and branched-chain Grignard reagents. The following reactions are illustrative of the effects of pronounced branching.



The mechanism of reaction between esters and RMgX compounds to give tertiary alcohols is also not clear. Grignard^{16b} interpreted the reaction as involving three stages, the first being addition to the carbonyl group.



¹⁵ Gilman, Woolley, and Wright, *ibid.*, **55**, 2609 (1933); Chute, Orchard, and Wright, *J. Org. Chem.*, **6**, 157 (1941).

¹⁶ (a) Whitmore and co-workers, *J. Am. Chem. Soc.*, **63**, 643 (1941). (b) Grignard *Compt. rend.*, **132**, 336 (1901); *Ann. chim. phys.*, **24**, 433 (1901).

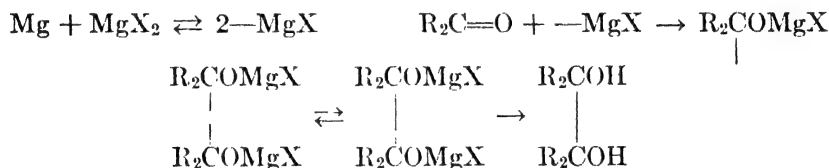
An alternative mechanism involves the intermediate formation of a ketone which then reacts with the RMgX compound to give the tertiary alcohol.



Ketones have been isolated from such reactions, and Boyd and Hatt¹⁷ carried out experiments to establish the transitory existence of ketones. These authors showed that, when esters are treated with Grignard reagents in the presence of an excess of magnesium, pinacols are among the reaction products. The pinacols are known to form in ether solution by interaction of a ketone and the binary system $(\text{MgX}_2 + \text{Mg})$.¹⁸ The necessary MgX_2 is present in all Grignard preparations and is also available from the following equilibrium which appears to hold for compounds having $-\text{MgX}$ attached not only to carbon but also to other elements like nitrogen, oxygen, and sulfur.



The formation of pinacol by the following sequence of reactions may then be interpreted as offering support for the existence of a ketone as an intermediate.



If it be granted that ketones are formed as intermediates, there remains the question whether they are formed from the ester by prior addition to the carbonyl linkage in accordance with reaction 4 of Grignard, followed by elimination of $\text{C}_2\text{H}_5\text{OMgX}$; or by the direct replacement of the ethoxy (or $\text{RO}-$) group by R' of the $\text{R}'\text{MgX}$ compound (reaction 7). Boyd and Hatt suggest the initial formation of a magnesium complex, the ketone being formed by the ready loss of ethoxy-magnesium halide.

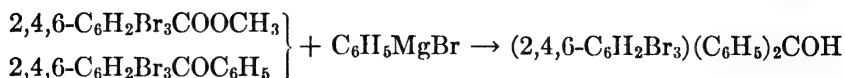
On other grounds, Morton and Peakes¹⁹ prefer the mechanism of Grignard because if ketones are intermediates one might expect to get better yields of tertiary alcohol from the ketone than from the ester, but such an expectation was not realized from their experiments.

¹⁷ Boyd and Hatt, *J. Chem. Soc.*, 898 (1927).

¹⁸ Gomberg and Bachmann, *J. Am. Chem. Soc.*, **49**, 236 (1927).

¹⁹ Morton and Peakes, *ibid.*, **55**, 2110 (1933).

They obtained a distinctly better yield of 2,4,6-tribromotriphenyl

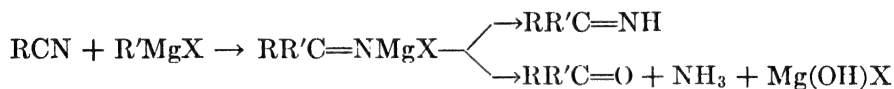


carbinol from methyl 2,4,6-tribromobenzoate than from 2,4,6-tribromobenzophenone.

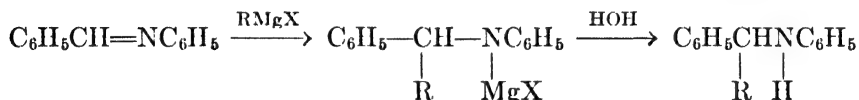
Whatever the mechanism of reaction, there is preliminary addition of some kind (possibly to give oxonium compounds), for in some cases the initial complex formed from ester and Grignard reagent regenerates the ester on treatment with water (p. 556).

The series of relative reactivities of some typical functional groups is very useful. First, it suggests possible combinations of functional groups in a polyfunctional type wherein preferential reactions with one group or another might be realized; and, second, the series is broadly applicable to other moderately reactive organometallic types which have been investigated.

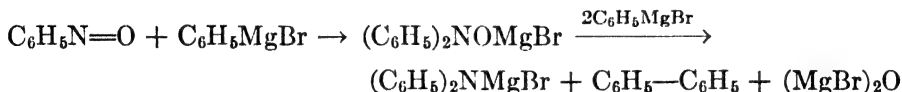
Cyanides give ketimines from which ketones are formed in the customary hydrolysis which concludes a Grignard reaction.



Azomethylene compounds like benzalaniline give secondary amines.



Reaction with the nitrosyl group attached to carbon as in nitroso-benzene is somewhat complex, but it appears that the chief course of reaction with phenylmagnesium bromide is the following:



the bromomagnesium diphenylamine giving diphenylamine on hydrolysis.

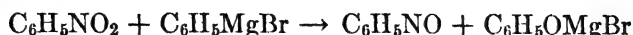
With a nitro compound like nitrobenzene, the complex reaction appears to proceed largely as follows:^{20a}



It is to be noted here that part of the phenylmagnesium bromide is oxidized to phenol, and the chemiluminescence which accompanies this reaction is undoubtedly due to such oxidation. The formation of

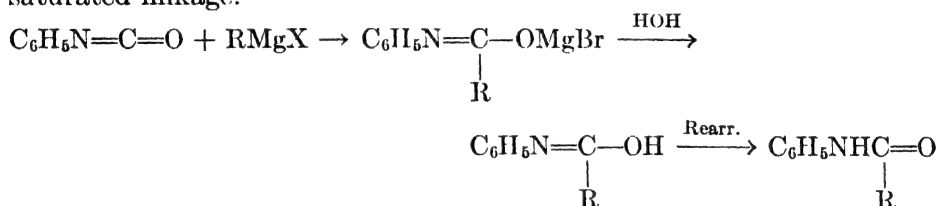
²⁰ (a) Gilman and McCracken, *ibid.*, **51**, 821 (1929). (b) Gilman, Kirby, and Kinney *ibid.*, **51**, 2252 (1929).

diphenylamine and biphenyl in both the nitrosobenzene and nitrobenzene reactions suggests that nitrosobenzene is an intermediate in the nitrobenzene reaction.



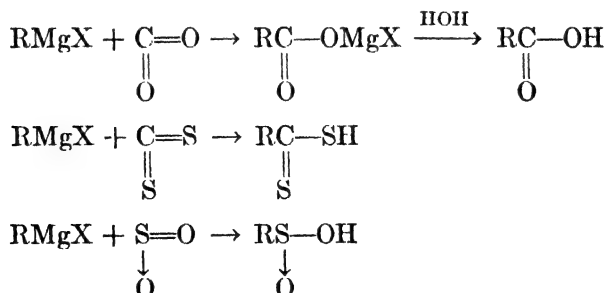
When alkylmagnesium halides are used, tetrasubstituted hydrazines are among the reaction products: for example, ethylmagnesium bromide and nitrobenzene give 1,2-diphenyl-1,2-diethylhydrazine, $(\text{C}_6\text{H}_5)(\text{C}_2\text{H}_5)\text{NN}(\text{C}_2\text{H}_5)(\text{C}_6\text{H}_5)$.

Compounds having two unsaturated linkages may be classified as (1) terminal or non-terminal cumulated unsaturated systems; (2) conjugated systems; and (3) systems having the unsaturated linkages separated by one or more carbon atoms. Systems having terminal cumulated unsaturation comprise types like ketenes ($\text{R}_2\text{C}=\text{C}=\text{O}$), isocyanates ($\text{RN}=\text{C}=\text{O}$), isothiocyanates ($\text{RN}=\text{C}=\text{S}$), and thionylamines ($\text{RN}=\text{S}=\text{O}$). In such systems, addition takes place predominantly, if not exclusively, under moderate conditions, to the terminal unsaturated linkage.^{20b}



The reaction with isocyanates proceeds smoothly, and phenyl and α -naphthyl isocyanates are among the reagents used to characterize RMgX compounds.²¹

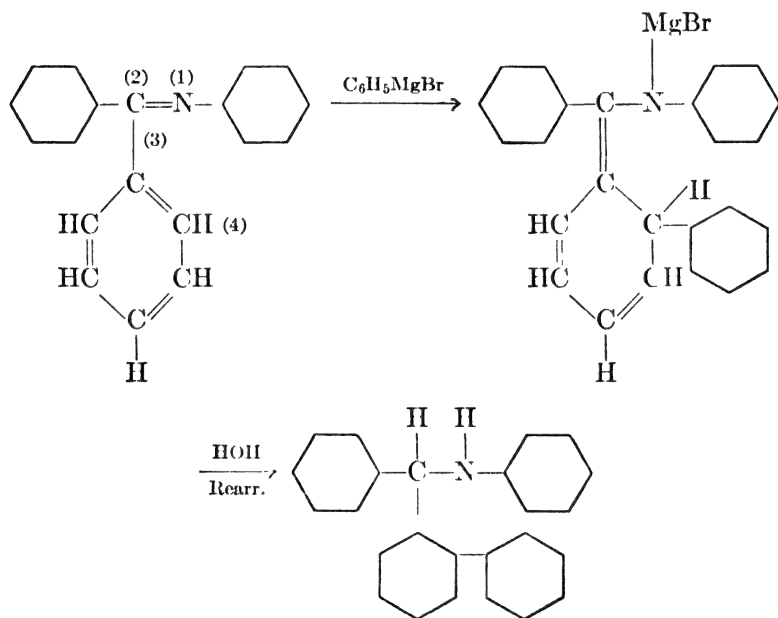
Non-terminal cumulated unsaturated systems, like $\text{RN}=\text{C}=\text{NR}$, generally give the reactions one would expect of the isolated simple unsaturated linkages. The very simple cumulated unsaturated linkages in compounds like carbon dioxide, carbon disulfide, and sulfur dioxide usually add but one molecule of Grignard reagent.



²¹ Schwartz and Johnson, *ibid.*, **53**, 1063 (1931); Gilman and Furry, *ibid.* **50**, 1214 (1928).

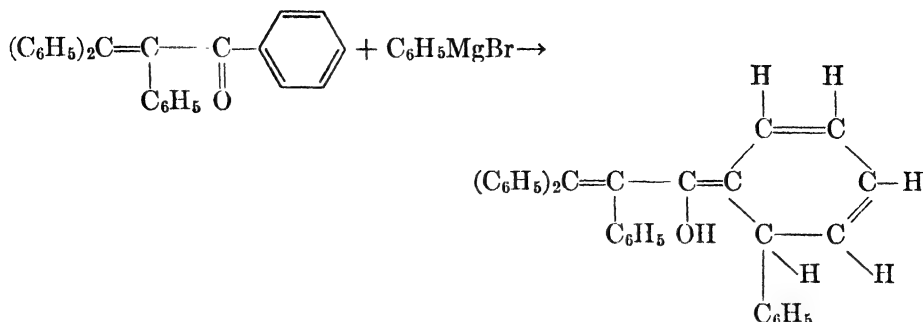
The carbon dioxide reaction or carbonation has been widely used both for the preparation of carboxylic acids and for the characterization of many organometallic compounds. In order to reduce secondary reactions leading to the formation of ketones and tertiary alcohols it is desirable to cool the mixture or to have the carbon dioxide in excess by spraying the Grignard reagent into an atmosphere of carbon dioxide. A simple procedure that provides cooling and an excess of carbon dioxide is to pour the Grignard reagent upon solid carbon dioxide.

Conjugated systems can undergo 1,2- or 1,4-addition, depending on the particular system and the Grignard reagent. The factors affecting 1,2- and 1,4-additions to conjugated systems are considered on p. 673. Grignard reagents have the unusual property of unlocking a conjugated system which is in part lateral and in part nuclear. With benzophenone-anil, for example, addition does not take place at the lateral $C=N$ — group; instead 1,4-addition occurs as follows: ^{20b}

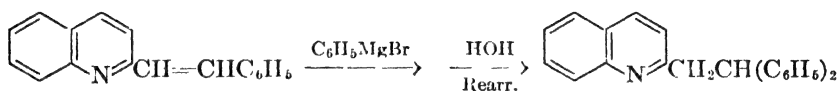


and *o*-phenylbenzohydrylaniline results. It is possible that steric factors are partly responsible for the 1,4-addition, inasmuch as it was previously shown that benzalaniline, $C_6H_5CH=NC_6H_5$, underwent lateral 1,2-addition to the $>C=N$ — linkage. The peculiar addition of $RMgX$ compound to a lateral-nuclear system is shown by some other compounds having such a system: for example, the addition of phenylmagnesium bromide to a highly phenylated unsaturated ketone,²²

²² Kohler and Nygaard, *ibid.*, **52**, 4128 (1930).

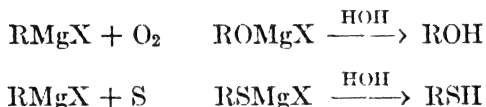


and to benzalquinaldine which has a lateral ethylenic linkage and a nuclear N=C linkage.²³



With systems having two unsaturated linkages separated by one or more carbon atoms, the normal 1,2-additions take place as in simple systems, and if there be an ethylenic or acetylenic linkage in such systems there is no 1,2-addition to these particular linkages. 1,6-Addition is uncommon (p. 696).

Reaction with Oxygen and Sulfur. The reaction with oxygen and sulfur may be considered as addition of the Grignard reagent to these elements.



It is interesting that, whereas oxidation of alkylmagnesium halides gives high yields of alcohols, the oxidation of arylmagnesium halides gives low yields of phenols. The unsatisfactory yields of phenols are undoubtedly associated with a secondary reaction of the Grignard reagent with ether peroxides formed from oxygen and diethyl ether.^{24a} There is no satisfactory explanation for the significant differences between the alkyl and aryl Grignard reagents on oxidation.

Inasmuch as the oxidation proceeds quite rapidly it is essential to exclude air in Grignard reactions which proceed slowly.^{24b} This is done conveniently by operating in an inert atmosphere like nitrogen.

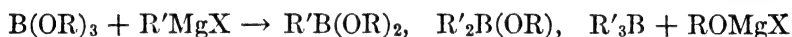
²³ Hoffman, Farlow, and Fuson, *ibid.*, **55**, 2000 (1933). (See, also, Allen and Overbaugh, *ibid.*, **57**, 1322 (1935), and Charrier and Ghigi, *Ber.*, **69**, 2211 (1936).

²⁴ (a) Wuyts, *Compt. rend.*, **148**, 930 (1909); Porter and Steel, *J. Am. Chem. Soc.*, **42**, 2650 (1920); Gilman and Wood, *ibid.*, **48**, 806 (1926); Müller and Töpel, *Ber.*, **72**, 273 (1939). (b) Goebel and Marvel, *J. Am. Chem. Soc.*, **55**, 1693 (1933).

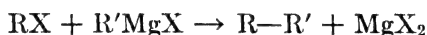
Oxidation of RMgX compounds by oxygen, peroxides, or many nitro compounds is accompanied by luminescence. In general, the chemiluminescence is greatest with arylmagnesium halides, and particularly with *p*-chlorophenylmagnesium bromide.

It is probable that the Grignard reagent is peroxidized initially. With sulfur there are formed not only mercaptans or thiophenols, in good yields, but also sulfides and polysulfides. Selenium and tellurium behave, in general, like sulfur.

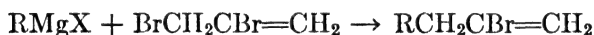
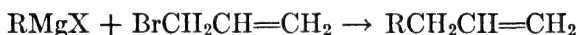
Reaction with Inorganic Esters. With the exception of alkyl esters of sulfonic acids, esters of oxygen acids react essentially by replacing an $-\text{OR}$ group of the ester by the R group of the Grignard reagent.



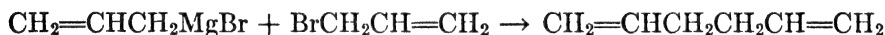
The reaction between alkyl halides and the Grignard reagent has been studied widely. The following replacement or coupling reaction



is confined largely to those alkyl halides having a highly reactive halogen. With allyl halide types the reaction is useful for the preparation of some unsaturated compounds.



In the preparation of allylmagnesium bromide it is obviously necessary to avoid a local excess of allyl bromide, for otherwise the initially formed allylmagnesium bromide would react to give diallyl.



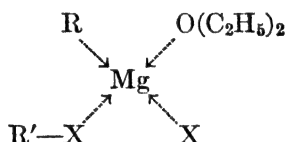
The slow addition of a dilute solution of allyl bromide to a large excess of fine magnesium makes it possible to prepare allylmagnesium bromide in 95 per cent yields. The fact that such special precautions to avoid an excess of RX compound are generally unnecessary in the preparation of RMgX compounds indicates that the coupling reaction is highly subordinated under moderate conditions. With organometallic compounds more reactive than Grignard reagents the coupling reaction may become the chief reaction, and this accounts for the Wurtz-Fittig reaction when RX compounds are treated with sodium or potassium. In such cases, as will be mentioned later in the organoalkali section, the extremely reactive organoalkali compounds couple readily with RX compounds having only a moderately reactive halogen.

The coupling reaction is not a simple union of the R of the alkyl halide with the R' of the Grignard reagent. Actually, three coupling

products are formed ($R-R'$, $R-R$, and $R'-R'$), for example, in the reaction between benzyl halides and methylmagnesium iodide.²⁵



The isolation of three coupling products suggests that free radicals, benzyl and methyl, are formed initially and then couple in the three possible combinations. However, the concept of free radicals to account for coupling to $R-R'$ compound appears unnecessary. What may happen is the formation of a coordination compound which is the first stage of all Grignard reactions²⁶ (p. 556).



Then the mobile electron shell surrounding the magnesium would provide for a sufficient approach of the R and R' ions to make unnecessary the postulate of intermediate free radicals or free ions²⁷ (p. 1863).

The reaction between alkyl sulfonates and the Grignard reagent is unusual in several respects. The overall reaction between dimethyl sulfate and aryl Grignard reagents



provides no mechanism for the several products.²⁸ The methyl halide must derive in considerable part from the following reaction, which is known to occur quite smoothly.



When one mole of dimethyl sulfate (and not the two moles required for complete reaction) is heated with one mole of an $RMgX$ solution, some of the Grignard reagent is, of course, recovered. This recovered Grignard reagent was shown by analysis to contain much more basic magnesium than halogen, which establishes the removal of part of the magnesium

²⁵ Späth, *Monatsh.*, **34**, 1965 (1913); Fuson, *J. Am. Chem. Soc.*, **48**, 2681 (1926); Ellingboe and Fuson, *ibid.*, **55**, 2960 (1933).

²⁶ Hess and Rheinboldt, *Ber.*, **54**, 2043 (1921); Meisenheimer, *Ann.*, **442**, 180 (1925); Gilman and Jones, *J. Am. Chem. Soc.*, **62**, 1243 (1940); **63**, 1162 (1941).

²⁷ Carothers and Berchet, *J. Am. Chem. Soc.*, **55**, 2807 (1933); Johnson, *ibid.*, **55**, 3029 (1933).

²⁸ (a) Cope, *ibid.*, **56**, 1578 (1934). (b) Suter and Gerhart, *ibid.*, **57**, 107 (1935); Rosander and Marvel, *ibid.*, **50**, 1491 (1928); Gilman and Heck, *ibid.*, **50**, 2223 (1928).

halide from the equilibrium: $2\text{RMgX} \rightleftharpoons \text{R}_2\text{Mg} + \text{MgX}_2$. Furthermore, the formation of an appreciable quantity of $\text{CH}_3\text{OSO}_2\text{OMgR}$ (a modified Grignard reagent) shows that reaction with RMgX proceeds by cleavage as RMg-X , and not as R-MgX as is generally true in Grignard reactions.

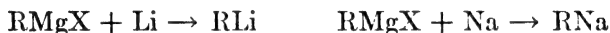


This finds additional support in the preparation of the organomagnesium methyl sulfate by interaction of dimethyl sulfate with R_2Mg compounds.



Accordingly, there is direct experimental evidence for reaction of dimethyl sulfate with magnesium halide and R_2Mg compound, and indirect analytical evidence for reaction with RMgX .^{28a} In short, each component of the Grignard equilibrium reacts with dimethyl sulfate. The reaction rates vary, however, and the methyl halide is produced largely from the rapid reaction with magnesium halide. Finally, it is interesting to note that the RMgX compound reacts differently from the R_2Mg compound.

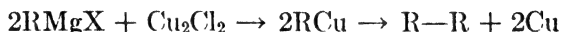
Reaction with Metals and Inorganic Salts. Grignard reagents react with those metals which generally form *more* reactive organometallic compounds.



However, the RMgX compounds give other organometallic compounds with those inorganic salts, generally the halides, which form *less* reactive organometallic compounds.



The organometallic product is not always isolated, for sometimes it is quite unstable thermally and gives rise to coupling products in a transformation which is of value in synthesis.



Halides of non-metals and of metalloids also generally undergo replacement of halogen by R of the RMgX compound.



An excess of Grignard reagent gives the simple compounds (R_3P and R_3As).

Secondary Reactions. Secondary reactions take place, in widely varying degrees, like most organic transformations. The kind and extent of the secondary reactions are influenced by the reactant, the particular Grignard reagent used, and the experimental conditions. In many cases it is possible to affect significantly the rate of various concurrent or consecutive reactions so that one or another of several reaction courses is made to predominate or to be exclusive. The effect of various factors in the most widely studied reaction of carbonyl compounds with Grignard reagents is strikingly illustrated on p. 646. Also, the effect of the kind of RMgX compound on 1,2- and 1,4-addition to conjugated systems is given on p. 673.

Varying reaction rates are particularly evident with different types of RM compounds. This is to be expected, for the differences in reactivity of RM compounds having different metals exceed the differences in reactivity of a series of RMgX compounds having different R and X groups. For example, benzalacetophenone can undergo 1,2- or 1,4-addition.

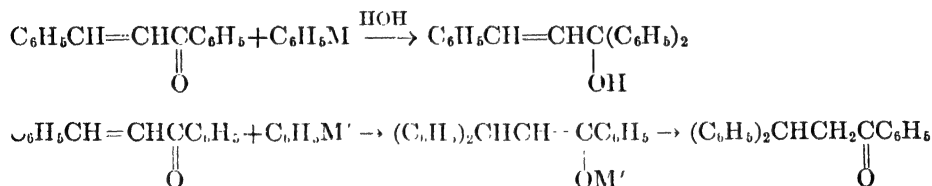


Table I illustrates the effect of various $\text{C}_6\text{H}_5\text{M}$ compounds on the extent of 1,2- and 1,4-additions.^{29a}

TABLE I

| RM | % 1,2-Addition | % 1,4-Addition |
|-------------------------------------|----------------|----------------|
| $(\text{C}_6\text{H}_5)_2\text{Be}$ | .. | 90 |
| $(\text{C}_6\text{H}_5)_2\text{Zn}$ | .. | 91 |
| $(\text{C}_6\text{H}_5)_3\text{Al}$ | .. | 94 |
| $\text{C}_6\text{H}_5\text{MnI}$ | .. | 77 |
| $\text{C}_6\text{H}_5\text{MgBr}$ | .. | 94 |
| $\text{C}_6\text{H}_5\text{Li}$ | 69 | 13 |
| $\text{C}_6\text{H}_5\text{Na}$ | 39 | 3.5 |
| $\text{C}_6\text{H}_5\text{CaI}$ | 45 | |
| $\text{C}_6\text{H}_5\text{K}$ | 52 | |

Azobenzene reacts in three general ways with $\text{C}_6\text{H}_5\text{M}$ compounds:^{29t} reduction to aniline; less extensive reduction to hydrazobenzene (reaction 1); and addition to give triphenylhydrazine (reaction 2).

²⁹ (a) Gilman and Kirby, *ibid.*, **63**, 2046 (1941). (b) Gilman and Bailie, *J. Org. Chem.* **2**, 84 (1937).

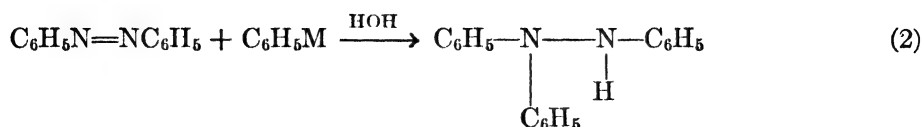
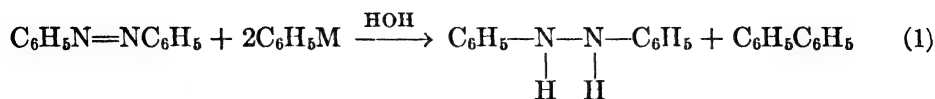


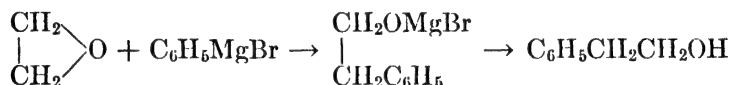
Table II lists the chief products obtained from azobenzene and some $\text{C}_6\text{H}_5\text{M}$ compounds.

TABLE II

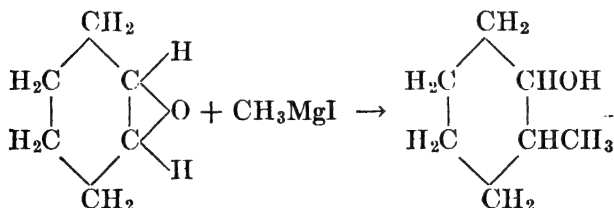
| <i>RM</i> | <i>Product</i> |
|-------------------------------------|--------------------|
| $(\text{C}_6\text{H}_5)_2\text{Zn}$ | Aniline |
| $\text{C}_6\text{H}_5\text{MnI}$ | Aniline |
| $(\text{C}_6\text{H}_5)_2\text{Be}$ | Hydrazobenzene |
| $\text{C}_6\text{H}_5\text{MgBr}$ | Hydrazobenzene |
| $\text{C}_6\text{H}_5\text{Li}$ | Hydrazobenzene |
| $\text{C}_6\text{H}_5\text{Na}$ | Hydrazobenzene |
| $\text{C}_6\text{H}_5\text{CaI}$ | Triphenylhydrazine |
| $\text{C}_6\text{H}_5\text{K}$ | Triphenylhydrazine |

Mention has been made of the participation of all three components of a Grignard mixture (RMgX , R_2Mg , and MgX_2) in the reaction with alkyl sulfonates. Another illustration of a side reaction of magnesium halide is the ring contraction observed with some alicyclic oxides.

Ethylene oxide is a useful reagent for introducing the β -hydroxyethyl group.

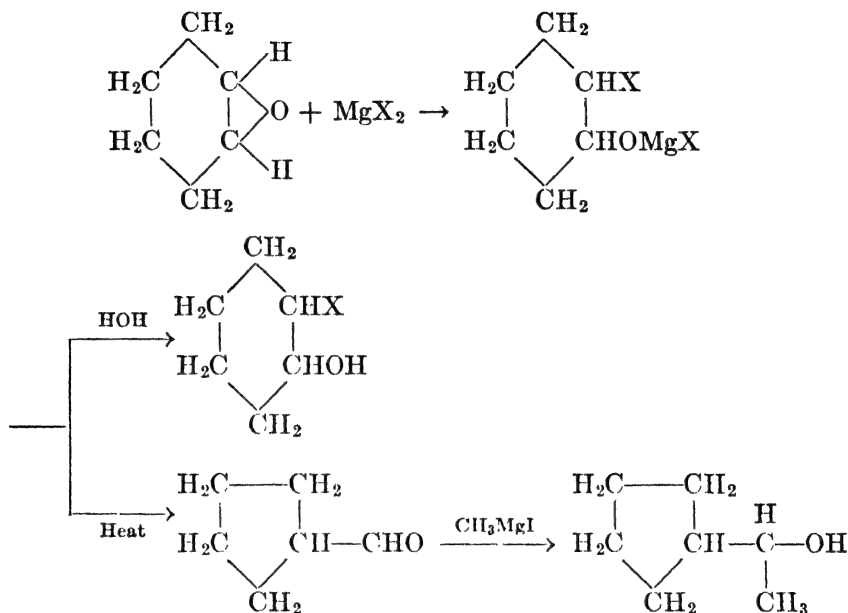


However, anomalous reactions take place in the reaction with some alicyclic oxides. Thus, the alcohol obtained from cyclohexene oxide and methylmagnesium iodide was supposed to be *cis*-2-methylcyclohexanol



until it was shown to be unlike the two isomeric 2-cyclohexanols subsequently prepared by the reduction of *o*-cresol. The anomalous Grignard reaction found an explanation in the observations that RMgX

compounds react with oxides and chlorohydrins of the cycloparaffin series to give ring contraction.^{30a} The supposed *cis*-2-methyleyclohexanol was in reality methyleyclopentylcarbinol, which results from the following sequential reactions:



The primary product of reaction between cyclohexene oxide and a Grignard reagent is the halohydrin derivative, which gives the smaller ring when strongly heated. Cyclopentanealdehyde is actually obtained by heating cyclohexene oxide with magnesium bromide in dry ether.^{30b}

On such a basis one might expect the halogen-free organomagnesium compound to add "normally" to cyclohexene oxide. The expectation is correct, for dimethylmagnesium and diethylmagnesium give 2-methylcyclohexanol and 2-ethylcyclohexanol, respectively.^{30c}

However, the problem is not simple, and the absence of magnesium halide is no necessary condition for the avoidance of ring contraction. For example, cyclohexene oxide and benzylmagnesium chloride give 2-benzylcyclohexanol.^{30d} This somewhat unexpected result cannot

³⁰ (a) Godchot and Cauquil, *Compt. rend.*, **186**, 375, 955 (1928); Vavon and Mitchovitch, *ibid.*, **186**, 702 (1928). (b) Bedos, *ibid.*, **189**, 255 (1929); Tiffeneau, *Bull. soc. chim.*, **3**, 1942 (1936). (c) Bartlett and Berry, *J. Am. Chem. Soc.*, **56**, 2683 (1934); Norton and Hass, *ibid.*, **58**, 2147 (1936); Cottle and Powell, *ibid.*, **58**, 2267 (1936). (d) Cook, Hewett, and Lawrence, *J. Chem. Soc.*, 71 (1936). For other reactions of oxides and RM compounds, see Wooster, Segool, and Allan, *J. Am. Chem. Soc.*, **60**, 1666 (1938), and Huston and Agett, *J. Org. Chem.*, **6**, 123 (1941). (e) Dean and Wolf, *J. Am. Chem. Soc.*, **58**, 332 (1936). (f) Coleman and Hauser, *ibid.*, **50**, 1193 (1928); Coleman and Blomquist, *ibid.*, **63**, 1692 (1941).

be attributed to the position of equilibrium with this Grignard reagent inasmuch as solutions of phenylmagnesium bromide, benzylmagnesium chloride, and β -phenylethylmagnesium bromide have about the same percentage of R_2Mg compound (75.8 per cent, 73.4 per cent, and 76.0 per cent, respectively) whereas only benzylmagnesium chloride gives the non-contracted cyclic product. A possible explanation is that dibenzylmagnesium is more reactive than benzylmagnesium chloride and magnesium chloride towards cyclohexene oxide, the Grignard equilibrium thus being disturbed by conversion of the less active $C_6H_5CH_2MgCl$ to $(C_6H_5CH_2)_2Mg$. In support of this interpretation is the fact that phenyllithium and phenylcalcium iodide, which are more reactive generally than the corresponding phenylmagnesium halides, do not give ring contraction with cyclohexene oxide.

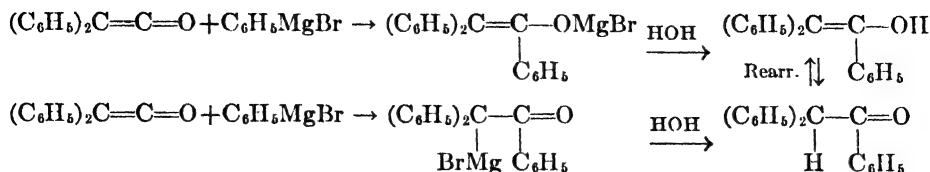
Incidentally, these several experiments illustrate some risks involved in making sweeping generalizations on the basis of a single organometallic compound or a small number of organometallic compounds. First, although benzylmagnesium chloride gives no ring contraction with cyclohexene oxide, there is ring contraction with the related halohydrin (2-chlorocyclohexanol). In this latter respect, therefore, benzylmagnesium chloride is like the other $RMgX$ compounds examined. Second, chloral reacts with alkyl and aryl Grignard reagents, including benzylmagnesium chloride, to give secondary alcohols.



However, other related phenyl-substituted alkylmagnesium halides like β -phenylethylmagnesium bromide, γ -phenylpropylmagnesium bromide, and δ -phenylbutylmagnesium bromide reduce chloral to trichloroethanol.^{30e} Third, even some Grignard reagents having the same R group, but unlike halogens, react at significantly different rates with some compounds.^{30f}

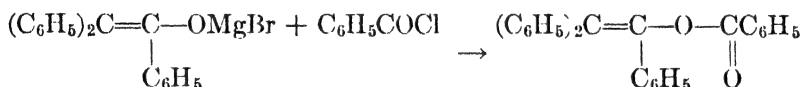
Reaction Mechanisms. Grignard reagents are polar compounds, and it is to be expected that the more satisfactory interpretations of their reaction mechanisms will be found to involve electronic concepts. Significant advances in this direction have been made with the chelation principles discussed elsewhere (p. 1879).

Gross interpretations of reaction mechanisms are of particular interest with polyfunctional compounds. The reaction between diphenylketene and phenylmagnesium bromide yields triphenylvinyl alcohol. The formation of this compound, however, throws no light on the mechanism of reaction, for the addition of phenylmagnesium bromide either to the carbonyl linkage or to the olefinic linkage would account for the product.

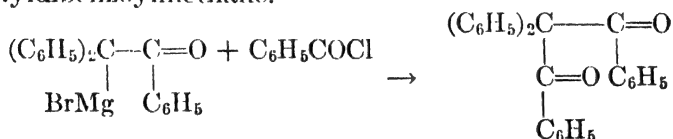


In a sense this was an impossible reaction when it was first carried out inasmuch as all reactions of ketenes were then explained on the basis of initial addition to the ethylenic linkage,^{31a} and Grignard reagents do not add to an ethylenic linkage.

One way of establishing the mode of addition is to prove the structure of the intermediately formed magnesium compound prior to hydrolysis and the attendant possibility of rearrangement. This was done^{31b} by treating the mixture with benzoyl chloride in order to tag or label the position of the —MgBr group. If addition takes place at the carbonyl group, the benzoate of triphenylvinyl alcohol should form.



If, however, addition occurs at the ethylenic linkage, the product should be diphenyldibenzoylmethane.



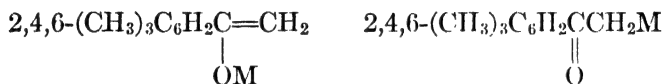
The product actually obtained was the benzoate of triphenylvinyl alcohol, thereby proving addition of the Grignard reagent to the carbonyl linkage.^{31b}

This method of establishing whether MgX is attached to carbon or to oxygen (or another element) is one which has been used extensively, and with particular success by Kohler and co-workers in their elegant work on the reaction of Grignard reagents with conjugated and other unsaturated systems (p. 673). Interestingly enough, Kohler in studies on the enolizing action of Grignard reagents has shown that the structure of some of the intermediate —MgX compounds cannot be unambiguously labeled in the manner set forth. That is, an —OMgX linkage may react with a labeling reagent to give a product which appears to show that the intermediate linkage was —CMgX. Such

³¹ (a) Staudinger, *Ann.*, **356**, 122 (1907). (b) Gilman and Heckert, *J. Am. Chem. Soc.*, **42**, 1010 (1920). (c) Kohler, Tishler, and Potter, *ibid.*, **57**, 2517 (1935). Fuson, Fugate, and Fisher, *ibid.*, **61**, 2362 (1939). (d) Gilman and Jones, *ibid.*, **63**, 1162 (1941).

—OMgX compounds will add to benzaldehyde, for example, exactly as simple Grignard reagents which have the —CMgX linkage.^{31c} The situation is much like that of sodium acetoacetic ester which has an —ONa linkage and yet undergoes alkylation to yield C-alkylated derivatives. In short, it is sometimes impossible to establish, by labeling-replacement reactions, the element to which the —MgX group is attached. Actually, the intermediate magnesium compounds are, like the Grignard reagent, ionized. The magnesium or —MgX group need not be attached to either oxygen or carbon, and the nature of the organic ion determines whether one gets essentially an —OMgX or a —CMgX replacement product.

There is a possibility that the —OM and —CM forms may be co-existent. For example, the metallic derivatives of acetomesitylene may be the following.^{31d}



It is now known that under some conditions a reactive C—M group may be present in a molecule containing also an otherwise reactive functional group (p. 538).

Rearrangement Reactions. It is not uncommon for Grignard reagents and Grignard reactions to show rearrangements. A simple illustration is the racemization that takes place when a Grignard reagent is formed from an optically active halide.^{32a} So-called abnormal products are most frequently encountered in reactions of Grignard reagents derived from allylic systems like those in benzylmagnesium halides and crotylmagnesium halides ($\text{CH}_3\text{CH}=\text{CHCH}_2\text{MgX}$). "Abnormal products" are not always formed, and the kind and extent of rearrangement vary markedly with the nature of the reactant. Some typical rearrangement reactions and their mechanisms are considered elsewhere (pp. 1009–1012, and 1879). The allylic rearrangement reactions are not peculiar to Grignard reagents but are shown by a great variety of organometallic types.^{32b} They have been most closely examined in Grignard reactions, however.

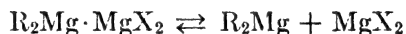
³² (a) Schwartz and Johnson, *J. Am. Chem. Soc.*, **53**, 1066 (1931); Pickard and Kenyon, *J. Chem. Soc.*, **99**, 65 (1911); Porter, *J. Am. Chem. Soc.*, **57**, 1436 (1935); Märker, Oakwood, and Crooks, *ibid.*, **58**, 481 (1936); Bergmann and Bondi, *ibid.*, **58**, 1814 (1936); Wallis and Adams, *ibid.*, **55**, 3838 (1933). For a related study of the action of lithium on an optically active chloride, see Tarbell and Weiss, *ibid.*, **61**, 1203 (1939). (b) Gilman and Nelson, *ibid.*, **61**, 741 (1939). (c) For some orienting references see Gilman and Harris, *ibid.*, **53**, 3541 (1931); Gilman and Kirby, *ibid.*, **54**, 345 (1932); Austin and Johnson, *ibid.*, **54**, 647 (1932); Jacobs, Cramer, and Weiss, *ibid.*, **62**, 1849 (1940); Campbell, Anderson, and Gilmore, *J. Chem. Soc.*, 819 (1940). (d) Young and co-workers, *J. Am. Chem. Soc.*, **58**, 289, 441 (1936); **60**, 900 (1938).

The so-called allylic rearrangements may not be true rearrangements. It was suggested some time ago that the anomalous reactions may actually be due in some cases to the co-existence of two structurally isomeric RM compounds.^{32c} Recent studies have lent experimental support to this interpretation.^{32d}

Constitution. Grignard reagents are almost always prepared in an ether, and only rarely in a tertiary amine. The reagent forms a coordination compound with such solvents. Inasmuch as a coordinating solvent or any solvent is not necessary for the preparation of Grignard reagents it is permissible to confine attention to the solvent-free complex. Jolibois^{33a} first suggested that the Grignard reagents should be designated as $R_2Mg \cdot MgX_2$ and not as $RMgX$. Then evidence^{33b} was presented for the following equilibrium



which has also found support in a series of electrolysis studies. Dioxane precipitates $RMgX$ and magnesium halide from ether solutions, leaving the R_2Mg compound, a procedure which incidentally is useful for the preparation of R_2Mg compounds. Also, dimethylmagnesium can be distilled, under reduced pressure, from methylmagnesium chloride.^{33c} Furthermore, a mixture of equivalent quantities of R_2Mg and MgX_2 behaves exactly like the corresponding Grignard reagent prepared from RX and magnesium. No reagent is known which will react with either $RMgX$ or R_2Mg and not with the other. Other than with alkyl sulfonates, there are no differences in kind of reaction with the mixed and simple organomagnesium compounds. Actually, therefore, in spite of good evidence for R_2Mg there is no rigorous support for $RMgX$. In this connection, one of the equilibria proposed for Grignard reagents is

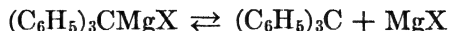


where the dot represents some form of molecular complex.^{33d} Inasmuch as the Grignard reagents are ionized, the most significant point to emphasize is that $RMgX$ compounds can ionize to $[R]^-$, $[MgX]^+$, $[RMg]^+$, $[X]^-$, and $[Mg]^{++}$.

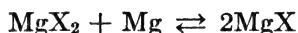
The percentage of R_2Mg in a Grignard solution varies both with the R group and the halogen.^{33b, d, e}

³³ (a) Jolibois, *Compt. rend.*, **155**, 353 (1912). (b) Schlenk and Schlenk, *Ber.*, **62**, 920 (1929); Gilman and Fothergill, *J. Am. Chem. Soc.*, **51**, 3149 (1929). (c) Gilman and Brown, *Rec. trav. chim.*, **48**, 1133 (1929). (d) Noller, *J. Am. Chem. Soc.*, **53**, 635 (1931). (e) Schlenk, Jr., *Ber.*, **64**, 734 (1931); Noller and Hilmer, *J. Am. Chem. Soc.*, **54**, 2503 (1932); Johnson and Adkins, *ibid.*, **54**, 1943 (1932); Bartlett and Berry, *ibid.*, **56**, 2683 (1934); Cope, *ibid.*, **56**, 1578 (1934); **57**, 2238 (1935); Noller and Raney, *ibid.*, **62**, 1749 (1940); Coleman and Blomquist, *ibid.*, **63**, 1692 (1941). (f) Gomberg and Bachmann, *ibid.*, **49**, 236, 2584 (1927).

Not only is there an equilibrium of the kind mentioned, but there may be the following equilibrium with triarylmethylmagnesium halides.



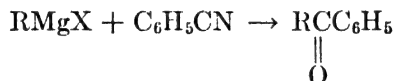
The possibility of an MgX radical or ion suggests the Gomberg-Bachmann magnesiumous halide equilibrium in those Grignard solutions containing free magnesium.^{33f}



Altogether, therefore, a Grignard solution may be a complex equilibrium mixture, which, for ordinary purposes, can be simply designated as RMgX.

Relative Reactivities. There are pronounced differences in the rates of reaction of Grignard reagents with a selected reactant, just as there are marked differences in the rates of reaction of a Grignard reagent with a series of reactants having unlike functional groups. The relative reactivities of some Grignard reagents have been determined in various ways. One procedure is to add a definite excess of reactant to the Grignard reagent and measure the time required to use up the RMgX compound, as evidenced by a negative color test with Michler's ketone.^{34a, b} The reactivities of some alkylmagnesium halides have been measured by the rate of evolution of gas when treated with an active hydrogen compound like indene.^{34c} The rates of reaction with an ester have been established by interrupting the reaction and determining the quantity of unused ester.^{34d} Another procedure is to permit two different Grignard reagents to compete for an insufficient quantity of benzophenone.^{34e}

Where comparisons can be made, the several series do not give wholly concordant results. The series established by the reaction with benzonitrile



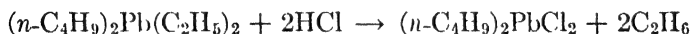
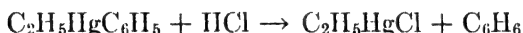
³⁴ (a) Gilman, Heck, and St. John, *Rec. trav. chim.*, **49**, 212 (1930). (b) Gilman, St. John, St. John, and Lichtenwalter, *ibid.*, **55**, 577, 588 (1936). (c) Ivanov, *Compt. rend.*, **196**, 491 (1933); *Bull. soc. chim.*, **51**, 619 (1932). (d) Vavon, Barbier, and Thiébaud, *ibid.*, **1**, 806 (1934). (e) Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936). (f) Kharasch, Reinmuth, and Mayo, *J. Chem. Education*, **13**, 7 (1936); Kharasch, Pines, and Levine, *J. Org. Chem.*, **3**, 347 (1938); Whitmore and Bernstein, *J. Am. Chem. Soc.*, **60**, 2626 (1938). (g) Gilman, Towne, and Jones, *J. Am. Chem. Soc.*, **55**, 4689 (1933). (h) Kipping, *J. Chem. Soc.*, 2365 (1928); Bullard, *J. Am. Chem. Soc.*, **51**, 3065 (1929); **53**, 3150 (1931). (i) Simons, *ibid.*, **57**, 1299 (1935). (j) Wooster and Mitchell, *ibid.*, **52**, 688 (1930). This last article directs attention to some apparent weaknesses of the acid-cleavage series. (k) Gilman and Towne, *ibid.*, **61**, 739 (1939). (l) Gilman and Moore, *ibid.*, **62**, 3206 (1940); Gilman, Moore, and Jones, *ibid.*, **63**, 2482 (1941).

is the most comprehensive so far examined. A part of the series follows, the numbers being average times in hours required for the complete reaction of RMgX with a definite excess of benzonitrile.^{34b}

| | | | |
|--|------|--|-------|
| $2,4,6\text{-(CH}_3)_3\text{C}_6\text{H}_2\text{MgBr}$ | 0 01 | $n\text{-C}_4\text{H}_9\text{MgBr}$ | 4 57 |
| $p\text{-CH}_3\text{C}_6\text{H}_4\text{MgBr}$ | 0 10 | $n\text{-C}_4\text{H}_9\text{MgI}$ | 7 50 |
| $\text{C}_6\text{H}_5\text{MgBr}$ | 0 31 | $\text{sec.-C}_4\text{H}_9\text{MgBr}$ | 11 65 |
| $\text{C}_2\text{H}_5\text{MgBr}$ | 0 85 | $\text{tert.-C}_4\text{H}_9\text{MgBr}$ | 25 5 |
| $n\text{-C}_4\text{H}_9\text{MgCl}$ | 7 35 | $\text{C}_6\text{H}_5\text{CH}_2\text{MgCl}$ | 1 60 |
| $\text{C}_6\text{H}_5\text{C}\equiv\text{CMgBr}$ 77.0 | | | |

The same order applies, of course, in competitive reactions. For example, when mesitylmagnesium bromide and phenylmagnesium bromide are allowed to compete for an insufficient quantity of benzonitrile the products are 92 per cent of benzoylmesitylene and 4 per cent of benzophenone; and in a competitive reaction using *n*-butylmagnesium bromide and phenylethynylmagnesium bromide the only ketone isolated was *n*-valerophenone, $n\text{-C}_4\text{H}_9\text{COC}_6\text{H}_5$.^{34b}

An inspection of the series reveals that the arylmagnesium halides are set apart from the alkylmagnesium halides, and this suggests a possible correlation between the relative reactivities of Grignard reagents and the ease of cleavage by acids of other organometallic compounds. When unsymmetrical organometallic compounds of mercury,^{34f} lead,^{34g} tin,^{34h} and germanium³⁴ⁱ are cleaved by halogens and halogen acids there is a preferential replacement of some of the radicals.



On the basis of the above two reactions it will be observed that the decreasing order of ease of cleavage of the three radicals is: C_6H_5 , C_2H_5 , $n\text{-C}_4\text{H}_9$. The series obtained by cleavage of unsymmetrical mercurials is discussed on p. 1071, and there is a satisfactory agreement between this series and those obtained by cleavage of other organometallic compounds.^{34j}

On the basis of the following typical reaction, the 2-furyl radical appears to be cleaved more rapidly than any other nuclear radical so far examined in the cleavage of unsymmetrical organometallic compounds by hydrogen chloride.^{34k}



The general acid-cleavage series is particularly useful, for it enables one to predict with some accuracy which radicals will be preferentially

cleaved by halogen acids, and cleavage by acids is one of the few common reactions of all RM compounds. However, there are definite and expected limitations in applying any one cleavage series to other series. The order or arrangement of radicals in a series depends not only on the nature of the radical, but also on the so-called cleavage agent, as well as on the central metallic element.³⁴ⁱ For example, the rates of cleavage of radicals in unsymmetrical organolead compounds by sodium in liquid ammonia are quite unlike the rates of cleavage of such compounds by hydrogen chloride in benzene or chloroform.

PERIODIC ARRANGEMENT OF ELEMENTS

| Group Family | I [A] [B] | II [A] [B] | III [A] [B] | IV [A] [B] | V [A] [B] | VI [A] [B] | VII [A] [B] | VIII |
|-----------------|--------------|---------------|----------------|---------------|--------------|---------------|----------------|----------|
| | Li | Be | B | C | N | O | F | |
| | Na | Mg | Al | Si | P | S | Cl | |
| | K | Ca | Sc | Ti | V | Cr | Mn | Fe Co Ni |
| | Cu | Zn | Ga | Ge | As | Se | Br | |
| | Rb | Sr | Y | Zr | Cb | Mo | Ma | Ru Rh Pd |
| | Ag | Cd | In | Sn | Sb | Te | I | |
| | Cs | Ba | La | Hf | Ta | W | Re | Os Ir Pt |
| | Au | Hg | Tl | Pb | Bi | Po | S5 | |
| | S7 | Ra | Ac | Th | Pa | U | | |

RELATIVE REACTIVITIES OF ORGANOMETALLIC COMPOUNDS

Inasmuch as organometallic compounds differ generally in degree or rate of reaction rather than in kind of reaction it is desirable to formulate at this place some broad generalizations concerning relative reactivities.³⁵ The expression "relative reactivities" is not intended to include two highly obvious properties of some RM compounds: namely, thermal instability and spontaneous inflammability. The highly unstable organosilver and organogold (RAu) compounds are of a relatively low order of so-called typical chemical reactivity, and ethylpotassium which starts to decompose at room temperature is extremely reactive. Trimethylboron and trimethylbismuth are spontaneously inflammable but not particularly reactive otherwise, whereas the methylalkali compounds like methylsodium are spontaneously inflam-

³⁵ Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

mable and also highly reactive generally. There appear, at this time, to be no correlations of thermal instability, spontaneous inflammability, and other chemical transformations. The illustrations just given are of RM compounds which are either highly reactive or of a relatively low order of reactivity. Organomanganese compounds are of moderate reactivity, but they are not only thermally unstable but also spontaneously inflammable.

A typical criterion of relative reactivity is addition to the carbonyl linkage. This reaction is shown not only by the thermally unstable organocopper and organosilver compounds, but also by the spontaneously inflammable organoberyllium and organoboron compounds as well as by the relatively unreactive organomercury and organolead compounds. The ten rules which follow are based generally on relative reactivities established by addition reactions to functional groups like the carbonyl and cyano.

First, the organometallic compounds in the A-families of the first three groups of the periodic table increase in reactivity with increasing atomic weight or atomic number. For example, in Group I, the order of increasing activity is: Li, Na, K, Rb, Cs. On this basis, when organometallic compounds will have been made of Element 87 it is to be expected that they will be the most reactive organometallic compounds. In Group II, the order of increasing activity appears to be: Be, Mg, Ca, Sr, Ba, Ra. Very little is known of organostrontium, organobarium, and organoradium compounds. In the A-family of Group III, the only organometallic compounds so far compared are those of boron and aluminum, and here the order of increasing reactivity is: B, Al.

The differences in reactivity are by no means regular, either in a selected group or when the members of one group are compared with the corresponding members of an adjacent group. For example, organosodium compounds are distinctly more reactive than organolithium compounds, but organopotassium compounds appear to be only slightly more reactive than organosodium compounds. Also, organomagnesium compounds are only slightly more reactive than organoberyllium compounds, whereas organocalcium compounds are decidedly more reactive than organomagnesium compounds. That is, in Group I the difference between the first and second organometallic types is greater than that between the second and third; but in Group II the difference between the first two types is less than that between the second and third.

Second, the organometallic compounds in the B-families of the first three groups generally decrease in reactivity with increasing atomic weight. For example, in Group I, the order of decreasing activity is:

Cu, Ag, Au; and in Group II: Zn, Cd, Hg. In Group III, however, the order of decreasing reactivity is: In, Ga, Tl.

Third, in the A-families of the first three groups, the organometallic compounds of one of the families of a selected group are more reactive than the corresponding organometallic compounds in the next higher group of that period. For example, the order of decreasing activity of the first members of the A-families of Groups I, II, and III is: Li, Be, B. In the next period, the order of decreasing activity is: Na, Mg, Al. Then we have the order: K, Ca, the organocompounds of Sc being as yet of unknown reactivity. Actually, the first element in an A-family of the first three groups gives an organometallic compound which is not only more reactive than that of the corresponding type in the next group, but also more reactive than the organometallic compounds derived from the second metal in the A-family of the next higher group. For example, organolithium compounds exceed organoberyllium and organomagnesium compounds in reactivity. Likewise, organoberyllium compounds are more reactive than organoboron and organoaluminum compounds.

Fourth, the least reactive organometallic compound derived from a metal of the A-family of one of the first three groups is more reactive than the most reactive organometallic compound containing a metal of the B-family of the same group. For example, organolithium compounds are more reactive than the corresponding organocopper compounds; and organoberyllium compounds are more reactive than the corresponding organozinc compounds.

Fifth, in the first three groups, an organometallic compound derived from a metal of the B-family is less reactive than the organometallic compound of a metal from the A-family of the next higher group. For example, organocopper compounds (B-family of Group I) are less reactive than organoberyllium compounds (A-family of Group II); and organozinc compounds (B-family of Group II) are less reactive than organoboron compounds (A-family of Group III).

The organometallic compounds of Group IV may be considered transitional between those of the three groups which precede and those of the three groups which follow Group IV. Actually, generalizations on the relative reactivities of organometallic compounds of Groups V, VI, and VII are essentially inversed counterparts of the generalizations concerned with Groups I, II, and III. These somewhat symmetrical formulations, if Group IV is pictured to form a sort of plane of symmetry, find an added emphasis in the A- and B-families of Group IV. The two families in Group IV appear to be less different than the two families in any other group. It must be admitted, however, that the

generalizations on organometallic compounds of Groups V, VI, and VII are less secure than those concerning Groups I, II, and III, for the simple reason that less is known of organometallic compounds in Groups V, VI, and VII.

Sixth, the organometallic compounds in the A-families of Groups IV, V, VI, and VII decrease in reactivity with increase in atomic weight of the metal. For example, in Group VII organomanganese compounds are distinctly more reactive than organorhenium compounds. This generalization is almost pure hypothesis because practically nothing is known of organometallic compounds of the A-families of Groups IV and V.

Seventh, the organometallic (or organometalloidal, or in some cases, merely the organic) compounds in the B-families of Groups IV, V, VI, and VII *increase* in reactivity with increase in atomic weight of the element. For example, in Group IV the order of increasing activity is: Ge, Sn, Pb; and in Group V the order is: As, Sb, Bi. Nothing is known of organopolonium compounds in Group VI, but the order of increasing reactivity of organic compounds of the other elements in this group, as evidenced by general chemical lability of the R groups, is: O, S, Se, Te. In Group VII the order of increasing activity is: F, Cl, Br, I. It will be recalled that some ascribe metallic characteristics to iodine.

Eighth, in Groups V, VI, and VII, the organometallic compounds of the A-family elements of a group are *less* reactive than the corresponding organometallic compounds of the next higher group of that period. For example, the order of increasing activity of the first members of the A-families in Groups V, VI, and VII is: V, Cr, Mn.

Ninth, the very meager information on organometallic compounds of the Fe to Pt series (Group VIII) may warrant the guess that these nine metals will form a series of organometallic compounds the reactivities of which will be patterned somewhat after the formulations proposed for the nine metals which comprise the B-families of the first three groups.

Tenth, an unsymmetrical organometallic compound of the type RMR' is more reactive than the symmetrical compound RMR , where M is the same metal. For example, $(\text{C}_6\text{H}_5)_2\text{Pb}(\text{C}_2\text{H}_5)_2$ is more reactive than either $(\text{C}_6\text{H}_5)_4\text{Pb}$ or $(\text{C}_2\text{H}_5)_4\text{Pb}$.

No reasonable formulation is possible at this time on the relative reactivities of "mixed" organometallic compounds (RMX) and "simple" RMR compounds. For example, RMgX compounds appear to be generally more reactive than R_2Mg compounds. However, R_2AlX and RAlX_2 compounds may be more or less reactive than R_3Al compounds, depending on the reactant selected for establishing relative reactivities.

Also, insufficient evidence is available to warrant generalizations on the relative reactivities of a series of organometallic compounds where the selected metal may have different valences: for example, R_2Pb , R_3Pb , R_4Pb . By reactivity in such compounds is not meant the tendency to add elements or groups to give a higher-valenced organometallic compound but rather the tendency of any R group to become detached from the metal and combine with some other element or group, particularly the carbonyl group.

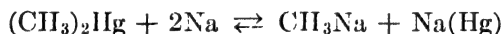
Inasmuch as the reactivities of organometallic compounds are influenced not only by the metal but also by the R group, it is to be expected that the ten generalizations owe whatever validity they may have to comparisons made with the same R group or R groups of equal effect. The rules may be inverted in some cases by a proper variation of R groups. For example, dimethylberyllium is less reactive than dimethylmagnesium, but dimethylberyllium is more reactive than diphenylethynylmagnesium $[(C_6H_5C\equiv C)_2Mg]$.

Broadly speaking, the relative reactivities of metallic hydrides and carbides agree with the formulations proposed for the relative reactivities of organometallic compounds.

GROUP I. A-FAMILY

[Li, Na, K, Rb, Cs]

The simpler organoalkali compounds are best prepared by the action of an alkali metal on the R_2Hg ³⁶ or R_2Zn compound.³⁷



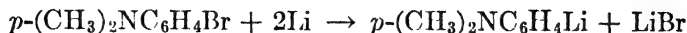
The organolithium compounds are exceptions, for these are obtained satisfactorily by procedures like those used for the preparation of Grignard reagents.³⁸ Actually, the RLi and $RMgX$ compounds admirably supplement each other; some RX compounds which form Grignard reagents with ease do not form any significant quantity of organolithium compound, using the simplified technique for the preparation of $RMgX$ compounds, whereas some halides which react very sluggishly with magnesium enter into prompt reaction with lithium to give excellent yields of RLi compounds. A case in point is the

³⁶ Schlenk and co-workers, *Ann.*, **463**, 1 (1928); **464**, 1 (1928).

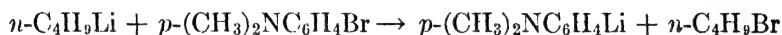
³⁷ Wanklyn, *Ann.*, **107**, 125 (1858); **140**, 211 (1866); Grosse, *Ber.*, **59**, 2646 (1926).

³⁸ Ziegler and Colonius, *Ann.*, **479**, 135 (1930); Gilman, Zoellner, and Selby, *J. Am. Chem. Soc.*, **54**, 1957 (1932); **55**, 1252 (1933); Gilman, Langham, and Moore, *ibid.*, **62**, 2327 (1940); Müller and Töpel, *Ber.*, **72**, 273 (1939).

preparation of *p*-dimethylaminophenyllithium in 95 per cent yield in ether solution by the following reaction.



It is possible to differentiate between a Grignard reagent and the corresponding RLi compound, and also between an alkyllithium compound and an aryllithium compound, by reactions designated as color test II.^{8b} This test is based on the following *prompt* halogen-metal interconversion reaction which is shown by alkyllithium compounds but not by aryllithium compounds or RMgX compounds.



The *p*-dimethylaminophenyllithium that results reacts with benzophenone to give a carbinol which on acidification turns red.

The organoalkali compounds have been roughly divided into three classes:³⁹ (I) The very highly reactive, colorless, simple alkyl M and aryl M types which are highly polar and insoluble in organic solvents. (II) The colored RM types which have the metal attached to a carbon in direct union with aromatic rings or a system of multiple bonds.



These, like the RM compounds of class I, are electrolytic conductors in many organic solvents, particularly in diethylzinc which itself is non-conducting. (III) Numerous organolithium compounds which are colorless, liquids or fusible solids, soluble in organic solvents, poor conductors, and generally only slightly polar.

As a group, the organoalkali compounds are the most reactive types, and the order of increasing reactivity is: RLi, RNa, RK, RRb, and RCs. This order has been established in several ways and particularly by the reaction rates of the phenylethynylalkali compounds, $\text{C}_6\text{H}_5\text{C}\equiv\text{CM}$, with an excess of benzonitrile, using the color test to determine when the RM compound was used up.⁴⁰ Benzonitrile was used because it contains a functional group which reacts slowly with organometallic compounds; and the phenylethynyl radical was selected because it gives a relatively unreactive organometallic compound when attached to any metal. An approximate idea of the relative reactivities follows; the times are in hours, and phenylethynylmagnesium bromide is included for comparative purposes.

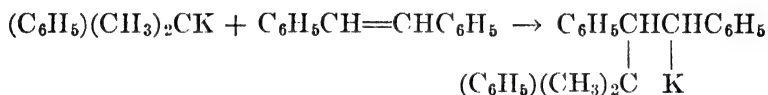
| | | | |
|--|-----|--|-----|
| $\text{C}_6\text{H}_5\text{C}\equiv\text{CMgBr}$ | 86 | $\text{C}_6\text{H}_5\text{C}\equiv\text{CK}$ | 4.4 |
| $\text{C}_6\text{H}_5\text{C}\equiv\text{CLi}$ | 60 | $\text{C}_6\text{H}_5\text{C}\equiv\text{CRb}$ | 3.9 |
| $\text{C}_6\text{H}_5\text{C}\equiv\text{CNa}$ | 6.8 | $\text{C}_6\text{H}_5\text{C}\equiv\text{CCs}$ | 2.9 |

³⁹ Ziegler, Crössmann, Kleiner, and Schäfer, *Ann.*, **473**, 1 (1929).

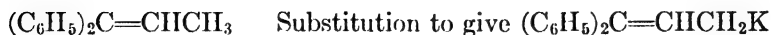
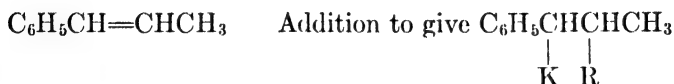
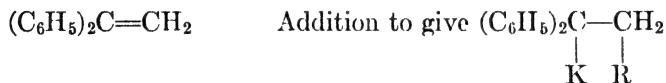
⁴⁰ Gilman and Young, *J. Org. Chem.*, **1**, 315 (1936).

In a broad sense, the organoalkali compounds show all the reactions of Grignard reagents. They differ, however, from RMgX and many other RM compounds in one important respect: they undergo addition to an olefinic linkage. Such addition is not peculiar to organoalkali compounds inasmuch as the highly reactive organocalcium compounds will likewise undergo such addition, but at a slower rate. It is most probable that the organic compounds of barium, strontium, and radium will be found to add to an olefinic linkage, for, if one may draw conclusions from present knowledge as well as from reasonable postulates, these together with the calcium compounds form a series that is more reactive than the RMgX type.

The first observed addition to an olefinic group was that of phenylisopropylpotassium to 1,2-diphenylethylene.⁴¹



In general, the most reactive organoalkali compounds of class I add readily; in class II those organoalkali compounds having more than one aromatic nucleus or unsaturated group attached to the carbon holding the metal add slowly or not at all or give rise to secondary reactions; and those in class III, like the alkyllithium compounds, add more slowly. Whether addition takes place or not depends, obviously, both on the RM compound and on the olefinic linkage. The unsaturated carbons of the olefinic linkage must, as a rule, be directly linked with an aromatic cycle or other unsaturated system, and the possibility of addition as well as of other reactions like substitution is influenced by both the number and kind of radicals. The following are some illustrations with phenylisopropylpotassium (RK).

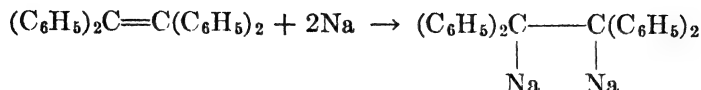


Addition reactions of organoalkali compounds to an olefinic linkage are intimately associated with other transformations, particularly the addition of alkali metals to olefinic linkages, the polymerization of unsaturated hydrocarbons by alkali metals and organoalkali com-

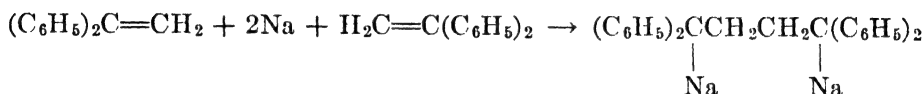
⁴¹ Ziegler and Bähr, *Ber.*, **61**, 253 (1928).

pounds, and hydrogenation by means of alkali metals and their amalgams.

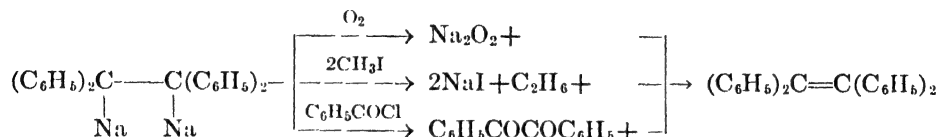
Two types of addition of alkali metals take place. One is a simple 1,2-addition,



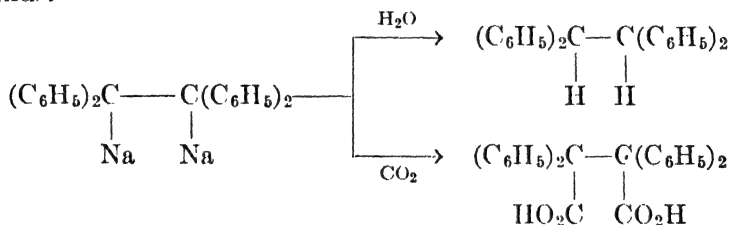
and the other has been termed a dimerizing addition,



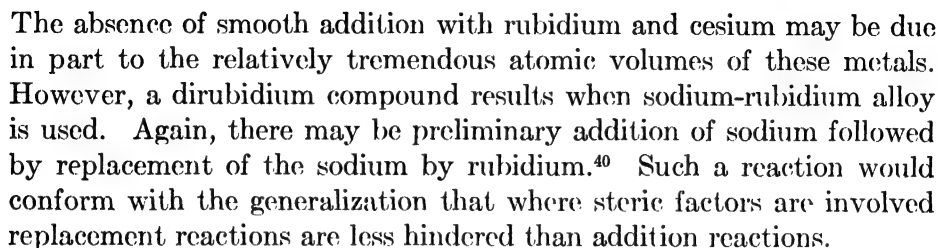
The dimerized addition products show the general reactions of Grignard reagents. However, the 1,2-addition products show few RMgX reactions; instead, they tend to regenerate the olefinic linkage.



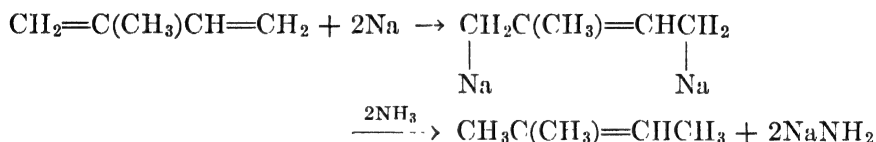
Water and carbon dioxide are among the small number of reagents which do not regenerate the double bond but react as with RMgX compounds.



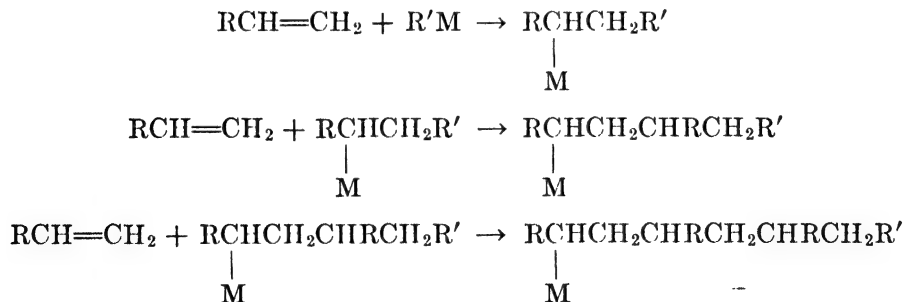
It is interesting to observe that the olefinic linkage in tetraphenylethylene, which is relatively unreactive to some addition reagents (particularly bromine, which does not add), undergoes prompt addition of sodium. Furthermore, the addition of sodium may be peculiar to this alkali metal, for under corresponding conditions lithium does not add. This may not be surprising in view of the lesser general reactivity of lithium. However, it is surprising that under the same conditions potassium likewise does not add. The dipotassium compound does form if sodium-potassium alloy be used, and this may be due to the initial addition of sodium followed by replacement by potassium in accordance with the general rule that the more reactive RM compound

$$\text{RMgX} + \text{Li} \rightarrow \text{RLi}$$


Olefins like styrene, 1-phenylbutadiene, butadiene, and isoprene are polymerized by sodium powder, the last two compounds giving sodium rubbers. The action of sodium on isoprene in liquid ammonia involves the preliminary 1,4-addition of sodium followed by hydrolysis to give 2-methylbutene-2.⁴²



Inasmuch as alkali metals add to an olefinic linkage to give an organoalkali compound, and since organoalkali compounds add to olefins to give more complex organoalkali compounds, it is understandable how a small quantity of alkali metal or organoalkali compound might convert many olefin molecules to large molecules or polymers.^{41, 43}



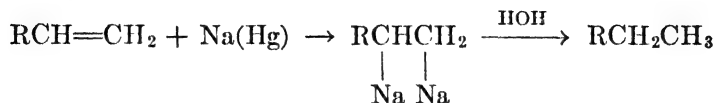
The previously mentioned organoalkali compounds which do not add to an olefinic linkage do not effect polymerization. With conjugated

⁴² Midgley and Henne, *J. Am. Chem. Soc.*, **51**, 1293 (1929).

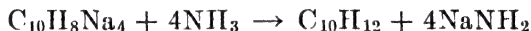
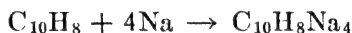
⁴³ Schlenk, Appenrodt, Michael, and Thal, *Ber.*, **47**, 473 (1914); Ziegler and Kleiner, *Ann.*, **473**, 57 (1929); Bergmann and co-workers, *Ann.*, **480**, 49, 59 (1930); *Ber.*, **64**, 1493 (1931); Ziegler, Grimm, and Willer, *Ann.*, **542**, 90 (1939).

systems like those present in butadiene and isoprene the polymerization probably involves 1,4-addition.

The reduction of some olefinic linkages by sodium-amalgam and water probably involves the preliminary addition of sodium, followed by hydrolysis of the resulting organosodium compound.⁴⁴



It is interesting to note that those hydrocarbons which are reduced by sodium in liquid ammonia add alkali metals or organoalkali compounds, and those which are not reduced do not undergo such addition.⁴⁵ More particularly, in the reduction of naphthalene by sodium in liquid ammonia to give tetrahydronaphthalene, there is not only the red color characteristic of the organoalkali compound but also the quantitative evidence that only four atoms of sodium react with each molecule of naphthalene, essentially irrespective of the quantity of excess metal present and the elapsed time of reaction.⁴⁶



These observations are not consistent with the alternative reduction by nascent hydrogen derived from sodium and ammonia.

Liquid ammonia is an excellent and convenient solvent for many reactions involving the alkali metals. There are, however, two notable differences between reactions in liquid ammonia and reactions in other media: (1) the highly concentrated solutions of alkali metals in liquid ammonia tend to give more extensive reactions; and (2) more side reactions occur in liquid ammonia due to participation of the solvent, as in ammonolysis and the formation of amines when halides are used.⁴⁷

Some substituted ammonium compounds are analogous to organoalkali compounds.⁴⁸ For example, triphenylmethyltetramethylam-

⁴⁴ Willstätter and Waldschmidt-Leitz, *Ber.*, **54**, 113 (1921).

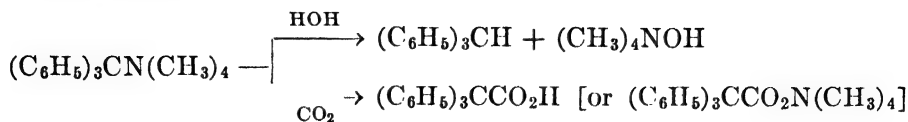
⁴⁵ Lebeau and co-workers, *Compt. rend.*, **157**, 223 (1913); **158**, 1514 (1914); **159**, 70 (1914).

⁴⁶ Wooster and co-workers, *J. Am. Chem. Soc.*, **53**, 179 (1931); **59**, 596 (1937). For recent studies on the addition of alkali metals to olefinic linkages see the following; Cappel and Fernelius, *J. Org. Chem.*, **5**, 40 (1940); Wright, *J. Am. Chem. Soc.*, **61**, 2106 (1939); Jeanes and Adams, *ibid.*, **59**, 2608 (1937); Scott, Walker, and Hansley, *ibid.*, **58**, 2442 (1936); Hückel and Bretschneider, *Ann.*, **540**, 157 (1939); and see Fernelius and Watt *Chem. Rev.*, **20**, 195 (1937), for a review of solutions of metals in liquid ammonia.

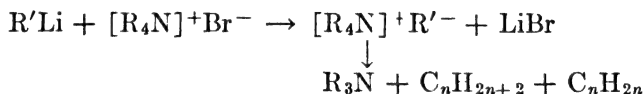
⁴⁷ Wooster and Ryan, *J. Am. Chem. Soc.*, **56**, 1133 (1934).

⁴⁸ Schlenk and Holtz, *Ber.*, **49**, 603 (1916); *Ber.*, **50**, 262, 274 (1917).

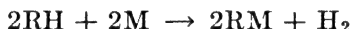
monium, $(\text{C}_6\text{H}_5)_3\text{CN}(\text{CH}_3)_4$, and benzyltetramethylammonium are colored, polar compounds which exhibit some typical reactions of the corresponding organoalkali compounds.



Attempts were made to prepare ammonium compounds having five closely related alkyl groups attached to nitrogen.⁴⁹ No pentaalkyl ammonium compound was obtained, and the tertiary amines isolated never contained an R group which was not initially present in the quaternary ammonium salt.



Conductivities of Organometallic Compounds. All organometallic compounds may be considered as salts derived from the weakly acidic RH compounds.



On such a basis, the organoalkali compounds should be and actually are the most polar RM types inasmuch as they are prepared, directly or indirectly, from the strongest bases. As strongly polar compounds, one would expect them not only to be good conductors but also to have the conductivities correlated with the strength of the bases from which they are derived. A particularly appropriate illustration is the study by Hein and co-workers⁵⁰ on the molar conductivities of ethylalkali solvates of diethylzinc. For comparative purposes the molar conductivities of 0.1 *N* aqueous solutions of the corresponding metal hydroxides at 18° are also given.⁵¹

**MOLAR CONDUCTIVITIES OF
C₂H₅M SOLVATES OF (C₂H₅)₂ZN**

| | |
|----------------------------------|------|
| C ₂ H ₅ Li | 0.13 |
| C ₂ H ₅ Na | 4.01 |
| C ₂ H ₅ K | 6.49 |
| C ₂ H ₅ Rb | 9.39 |

**MOLAR CONDUCTIVITIES OF
MOH**

| | |
|------|-------|
| LiOH | 74.5 |
| NaOH | 195.3 |
| KOH | 213 |
| RbOH | 213.3 |

⁴⁹ Hager and Marvel, *J. Am. Chem. Soc.*, **48**, 2689 (1926).

⁵⁰ Hein, *Z. Elektrochem.*, **28**, 469 (1922); Hein, Petzchner, Wagler, and Segitz, *Z. anorg. allgem. Chem.*, **141**, 161 (1924); Hein and Segitz, *ibid.*, **158**, 153 (1926).

⁵¹ "International Critical Tables," McGraw-Hill Book Co., New York (1929), Vol. VI pp. 246-253.

The splendid correlation between conductivities and relative reactivities of the ethylalkali compounds would seem to promise a high usefulness for this method of comparing relative reactivities. However, there are two general reasons for a restricted applicability of this procedure. First, even though the organoalkali compounds are the best conductors and (with the exception of RM compounds derived from the alkaline-earth metals) the only types that conduct adequately for the purposes in hand, they cannot generally be examined in this way. Their thermal instability precludes measurements in the fused state, and their insolubility together with high reactivity markedly limit the number of appropriate solvents. Second, the promise held out by the ethylalkali compounds is not sustained generally because of disturbing anomalous results. For example, phenylsodium in dimethylzinc does not conduct at all, whereas phenyllithium which is distinctly less reactive chemically does conduct. Also, the order of conductivities in a series having a selected metal but different R groups does not always follow either the order of chemical reactivities or the order established by conductometric methods for RM compounds having corresponding R groups attached to a different metal.

The use of diethylzinc to prepare solvates of the ethylalkali compounds for conductivity studies suggests that diethylzinc is a non-conductor. This is the fact. The same is true of the trialkylaluminum compounds, which, like dialkylzinc compounds, have found extensive application as a modified medium for measuring conductivities of the more reactive RM types. If the moderately reactive organoaluminum compounds do not conduct, it is understandable why the distinctly less reactive organocadmium and organomercury compounds are non-conducting. It should be emphasized that in all this the simple and not the mixed organometallic compounds are considered. The mixed salts like RMgX and the corresponding bases, RMOH , are as a rule good conductors. In such cases, however, it is probable that no significant ionization of the R-Metal linkage is involved.

The conduction of organometallic compounds follows Faraday's law. The metal is deposited on the cathode; and the R group, which is actually involved as an anion in the transport of the current, is discharged at the anode to give the coupling (R-R) or disproportionation products [$\text{R(+H)} + \text{R(-H)}$] or both.

Solvents of high dielectric constant are most suitable for such studies, and this applies to pyridine⁵² and particularly to liquid ammonia.⁵³

⁵² Ziegler and Wollschitt, *Ann.*, **479**, 123 (1930).

⁵³ Kraus, "The Properties of Electrically Conducting Systems," Chemical Catalog Co., New York (1922); Kraus and Johnson, *J. Am. Chem. Soc.*, **55**, 3542 (1933).

However, with salts like the Grignard reagents the usual solvent, ether, is quite satisfactory, and liquid ammonia is totally unsuitable because of its active hydrogens. Considerable work, particularly by Evans,⁵⁴ is being done on conductivity studies of RMgX compounds, and attention has already been directed to the bearing of such studies on the constitution of Grignard reagents.

Conductivity studies suggest the possible use of the electromotive series of the metals as a means of correlating relative reactivities, the more electropositive metals forming the more polar and more reactive RM compounds. In a general way, there is a correlation, but some of the exceptions are striking. If attention be confined to the alkali metals and calcium the following segment of the e.m.f. series results.⁵⁵

| | | | |
|----|-------|-------|-------|
| Li | 2.959 | K | 2.924 |
| Rb | 2.925 | Ca | 2.76 |
| Na | | 2.714 | |

It is at once evident that lithium is entirely out of line in the sense that the above series might lead to the expectation that RLi compounds would be the most reactive of the organoalkali compounds, whereas actually they are the least reactive. Also the organocalcium compounds should be more reactive than the organosodium compounds, but they are often less reactive; and diethylcalcium has been reported as completely non-conducting in diethylzinc, whereas ethylsodium is a good conductor.

Ionization Potentials of Metallic Atoms. It has been suggested⁵⁶ that the ionization potentials of metallic atoms provide a better correlation with the relative reactivities of RM compounds than either conductivities or the electromotive series. The lower the ionization potential of the metal, in a given group or subgroup, the more reactive will be its simple* organometallic compounds. For example, the ionization potentials⁵⁷ of the alkali metals are: Li = 5.36; Na = 5.12; K = 4.32; Rb = 4.16; Cs = 3.87. This is exactly the inverse relationship of the relative reactivities of the corresponding RM compounds.

Another pertinent illustration is the relative reactivities of the triphenyl derivatives of indium, gallium, and thallium. The ionization potentials of the metals in volts are: In = 5.76; Ga = 5.97; Tl = 6.07.

⁵⁴ Evans, Pearson, and Braithwaite, *J. Am. Chem. Soc.*, **63**, 2574 (1941); Konduirev, *Ber.*, **58**, 459 (1925); French and Drane, *J. Am. Chem. Soc.*, **52**, 4904 (1930); Duval, *Compt. rend.*, **202**, 1184 (1936).

⁵⁵ "International Critical Tables," McGraw-Hill Book Co., New York (1929), Vol. VI, p. 322.

⁵⁶ Gilman and Jones, *J. Am. Chem. Soc.*, **62**, 2353 (1940).

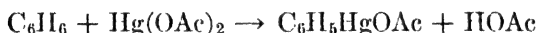
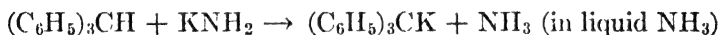
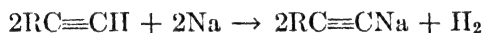
* Where only R groups and no salt-forming or acid radicals are attached to the metal.

⁵⁷ Latimer, "The Oxidation States of the Elements and Their Potentials in Aqueous Solutions," Prentice-Hall, New York, N. Y. (1938), p. 14.

Here, too, there is an inverse relationship with chemical reactivities of the corresponding R_3M compounds (p. 555).

There are exceptional cases which do not permit exact correlations of chemical reactivities with ionization potentials. All that can be said at this time is that the broad rules previously formulated on the basis of groups and families of the periodic table are most useful because they have the fewest exceptions.

Acidic Hydrogens and Metalation. Inorganic salts are commonly prepared by interaction of an acid with a metal, a base, or a salt. The same general reactions can be used for the preparation of RM compounds from the very weakly acidic hydrocarbons.



Inasmuch as RM compounds have properties of salts, they react with a weak acid (RH) to form another salt and another acid.



These several reactions involving the replacement of an acidic hydrogen by metal to give a true organometallic compound illustrate transformations designated as metalation.

It is clear that both the possibility of metalation and the rate of metalation are influenced by the strength of the acid and by the strength of the base or other metalating agent. The particular organic acids under immediate consideration are the extremely weak acids (RH), for which the usual methods of determining ionization constants are not applicable. Inasmuch as the metalation of an RH compound by an RM compound is influenced both by the strength of the acid and the polarity of the salt, it appears reasonable to expect that the reaction might be used to measure relative acidities of the very weak acids and relative polar characteristics or reactivities of the salts or RM compounds.

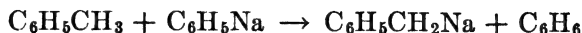
Benzene is metalated by ethylsodium to give phenylsodium in a reaction first studied by Schorigin.⁵⁸



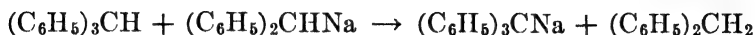
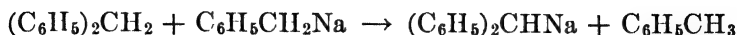
This reaction illustrates the displacement of sodium from a salt of the relatively weaker acid (C_2H_6) by the relatively stronger acid (C_6H_6)

⁵⁸ Schorigin, *Ber.*, **41**, 2711 (1908); **43**, 1938 (1910).

In like manner, a lateral hydrogen in toluene is shown to be more acidic than a nuclear hydrogen in benzene.



From the following additional metathetical reactions

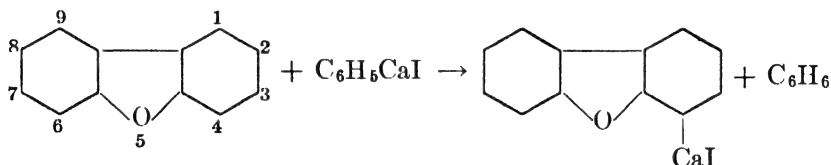


it follows that the order of increasing acidities of the several RH compounds is:

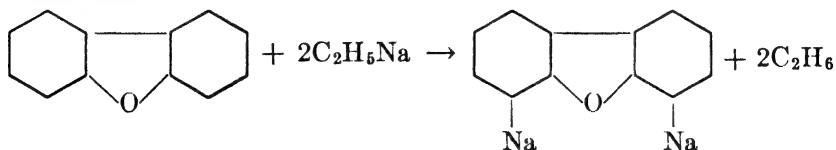


It has been found possible to arrange a series of extremely weak acids on a scale by using the general procedure just indicated,⁵⁹ and with some aromatic types it was found that phenyldimethylmethane, $\text{C}_6\text{H}_5(\text{CH}_3)_2\text{CH}$, was much weaker than phenylacetylene, $\text{C}_6\text{H}_5\text{C}\equiv\text{CH}$ (p. 1035). The method can also be used to compare the relative acidities of RNH_2 , ROH , and RSH compounds, all of which are less acidic, of course, than carboxylic and sulfonic acids.

In like manner, it is possible to compare the salts or RM compounds. For example, the Grignard reagent metalates dibenzofuran with difficulty, but organocalcium and organoalkali compounds effect metalation readily.



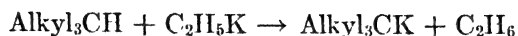
On such a basis, the organocalcium and organoalkali compounds are more saline or more polar than RMgX compounds. And because RLi compounds effect only monometalation whereas RNa compounds effect dimetalation



a means is available of corroborating, in this case, the greater polarity or reactivity of the RNa compound. Under like conditions, the RK com-

⁵⁹ Conant and Wheland, *J. Am. Chem. Soc.*, **54**, 1212 (1932); McEwen, *ibid.*, **58**, 1124 (1936).

pounds give more dimetalation than the less reactive RNa compounds. The highly reactive organoalkali compounds can be arranged in a series by extending the metalating reactions to uncommonly weak *aliphatic* acids like Alkyl_3CH .



Theoretically it would not be surprising to find the most reactive alkali metal, Element 87, progressively metalating methane to give a carbide.

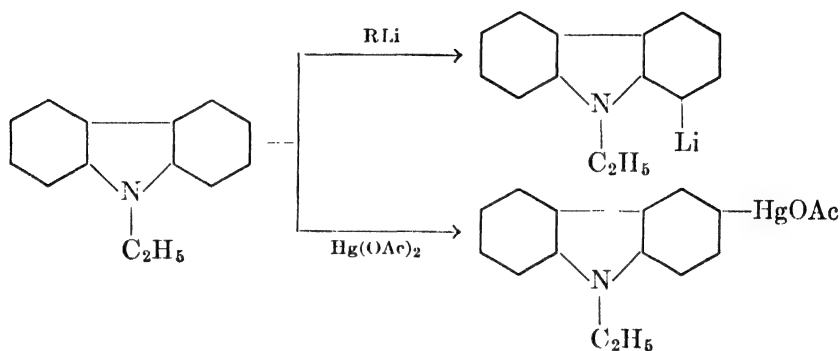


In short, hydrogen in any molecule is acidic in the sense that it will probably be found to be replaceable by a metal.

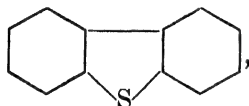
The less reactive organometallic compounds can also be arranged in a series if stronger acids be used. For example, RMgX compounds react with active hydrogens attached to oxygen, sulfur, nitrogen, and triply bonded carbon ($\text{RC}\equiv\text{CH}$). Under selected conditions, the R_3Al compounds react with the several types of active hydrogens just mentioned, but not with true acetylenes; R_2Zn compounds react with RNH_2 and the other types of active hydrogen compounds, but not appreciably with R_2NH compounds; and R_2Cd compounds react neither with true acetylenes nor with amines, but react with the other types of active hydrogen compounds. This illustrates not only a procedure for differentiating various types of active hydrogen but also a method of arranging the RM compounds on the basis of their reactions with active hydrogen compounds. The decreasing activities of these RM compounds toward active hydrogen compounds are: R Alkali, RCaX , RMgX , R_2Zn , R_3Al , R_2Cd ; and the decreasing strengths of the acids are: RSH , ROH , RNH_2 , R_2NH , $\text{RC}\equiv\text{CH}$, RH . The series of RM compounds obtained by reaction with active hydrogen types is not exactly that obtained by reaction of RM compounds with a functional group like carbonyl. Also the series of active hydrogen types is not always consistent. For example, triethylbismuth reacts with RSH compounds but with none of the other active hydrogen types including some carboxylic acids.

The even less reactive types like R_4Sn and R_4Pb can be differentiated by the use of stronger acids. For example, the rate of cleavage of R_4Pb compounds by means of trichloroacetic acid is much greater than that of the corresponding R_4Sn compounds, which on other grounds are known to be less reactive. Also, hydrogen chloride at 0° will cleave tetraphenyltin at a measurable rate for kinetic studies, but at a too rapid rate if tetraphenyllead be used.

In metalation reactions, the hydrogen or hydrogens replaced by metals may be the same or different, depending on the compound being metalated and on the metalating agent. When dibenzofuran is mono-metalated the same 4-hydrogen is replaced, irrespective of the metalating agent: alkali metal, RM compound, $\text{Hg}(\text{OAc})_2$. However, a related type, N-ethylcarbazole, metalates in different positions depending on the metalating agent.^{60a}



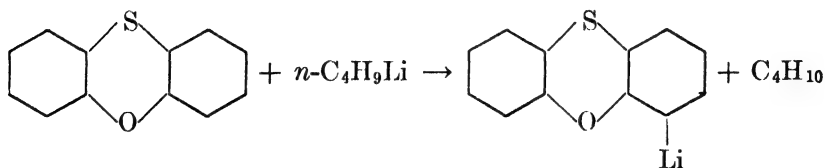
An even more striking example is the metalation of dibenzothiophene,



which is monometalated in different positions by the

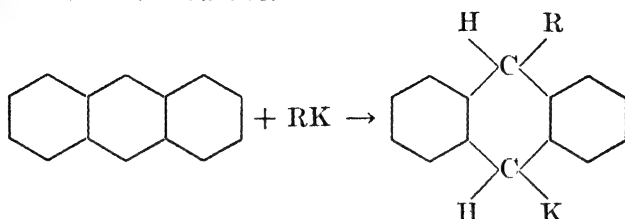
otherwise closely related phenyllithium and phenylcalcium iodide. This indicates highly selective reactions of synthetic value, particularly when it is considered that metalations frequently involve the replacement of hydrogens unaffected by other nuclear substitution reactions like halogenation, nitration, sulfonation, and the Friedel-Crafts reaction.

In general, metalation takes place predominantly in a position *ortho* to the hetero element; and the order of decreasing influence of some hetero elements is: O, S, N, P, As.^{60b} A simple illustration is the metalation of phenoxathiin.



⁶⁰ (a) Gilman and Kirby, *J. Org. Chem.*, **1**, 146 (1936); Miller and Bachman, *J. Am. Chem. Soc.*, **57**, 2447 (1935); Gilman, Stuckwisch, and Kendall, *ibid.*, **63**, 1758 (1941); (b) Gilman and Bebb, *ibid.*, **61**, 109 (1939); Gilman, Van Ess, Willis, and Stuckwisch, *ibid.*, **62**, 2606 (1940). (c) Ziegler and Bähr, *Ber.*, **61**, 253 (1928). (d) Gilman and Cook, *J. Am. Chem. Soc.*, **62**, 2813 (1940). (e) Gilman and Bradley, *ibid.*, **60**, 2333 (1938).

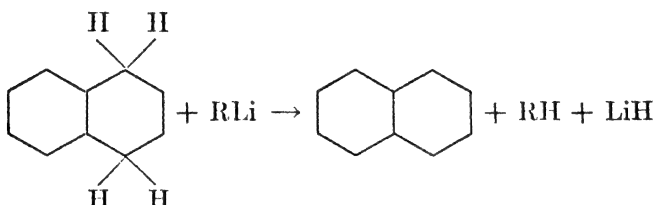
Aromatic nuclei and RM compounds do not always react to give metalation reactions. Two other transformations might be mentioned. One is addition as in anthracene.



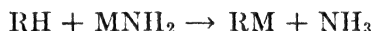
The other ^{60c} is dimerization as with phenanthrene.



It is also possible to metalate phenanthrene in the 9-position by means of alkyllithium compounds.^{60d} With some partially hydrogenated polynuclear types like 1,4-dihydronaphthalene there is smooth dehydrogenation to naphthalene.^{60e}



In connection with lateral and not nuclear metalation of hydrocarbons by alkali amides in liquid ammonia,

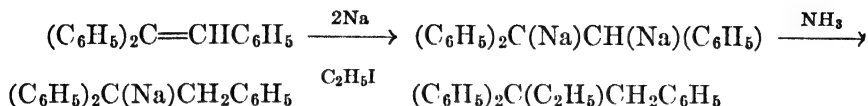


it was noticed that organoalkali compounds form only with those hydrocarbons having a benzohydryl group, $(\text{C}_6\text{H}_5)_2\text{CH}-$.

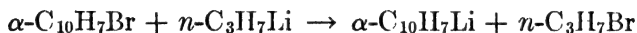


No reaction was observed with compounds like $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)_2$, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$, $(\text{C}_6\text{H}_5)_3\text{CCH}_3$. The "benzohydryl rule" growing out of these studies has been used with success in interpreting some reactions. For example, when 1,1,2-triphenylethylene is treated with

sodium, the disodium compound initially formed undergoes partial ammonolysis to give a monosodium compound. This compound should have the sodium attached to the benzohydril carbon, and this interpretation was shown to be correct by replacing the sodium by ethyl to give a hydrocarbon of established structure.⁶¹



Halogen-Metal Interconversion Reactions.^{62a} The following halogen-metal interconversion reaction occurs in a 97 per cent yield.



There are numerous variations of such reactions. In general, the most useful halides are those containing bromine or iodine; and, although halogen-metal interconversions have been effected with a variety of RM compounds, organolithium compounds are most effective.

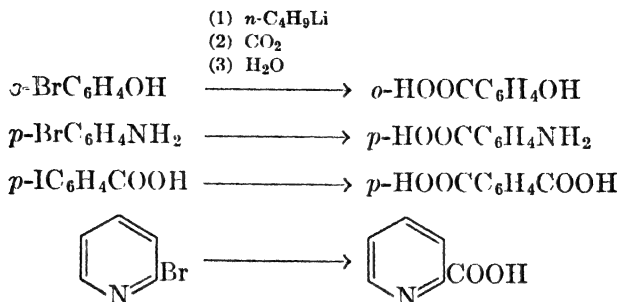
The reaction is of particular value in the synthesis of some reactive RM compounds which either cannot be prepared at all or can be prepared only with difficulty and in highly unsatisfactory yields. For example, although no appreciable quantity of an RMgBr or RLi compound can be prepared directly from 3-bromo-2,4,5-triphenylfuran or 2-bromo-3,4,6-triphenylpyridine, the respective RLi compounds are readily prepared in satisfactory yields by halogen-metal interconversions with *n*-butyllithium.



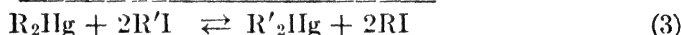
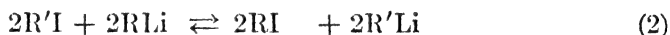
Of greater significance is the formation of RLi compounds from compounds having otherwise reactive functional groups like —OH, —NH₂, —COOH, and =C=N—. The yields of acids formed in the following transformations average in excess of 70 per cent.

⁶¹ Wooster and Mitchell, *J. Am. Chem. Soc.*, **52**, 688 (1930).

⁶² (a) Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938); Wittig, Pockels, and Dröge, *Ber.*, **71**, 1903 (1938); Gilman, Langham, and Jacoby, *J. Am. Chem. Soc.*, **61**, 106 (1939); Gilman and Moore, *ibid.*, **62**, 1843 (1940); Wittig and co-workers, *Ber.*, **73**, 1197 (1940); Gilman, Langham, and Moore, *J. Am. Chem. Soc.*, **62**, 2327 (1940); Gilman and Spatz, *ibid.*, **62**, 446 (1940); **63**, 1553 (1941). (b) Gilman and Jones, *ibid.*, **63**, 1439, 1441, 1443 (1941).



The halogen-metal interconversion reaction not only provides a reasonable mechanism for some earlier so-called anomalous reactions between RM compounds and reactants having halogens or pseudo-halogens but also explains the function of traces of RLi compound as a catalyst in halogen-metal interconversions with *unreactive* RM types.^{62b} For example, reaction 3 takes place only in the presence of catalytic quantities of RLi compound. The function of the RLi compound follows from the established reversibility of reactions 1 and 2, which add up to reaction 3.

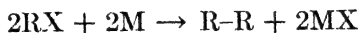


In general, a metal-metal interconversion reaction like 1 proceeds more rapidly than a halogen-metal interconversion, and this in turn goes at a greater rate than a hydrogen-metal interconversion or metalation reaction.

The Wurtz-Fittig Reaction (p. 385). The reaction between a halide and a metal is influenced both by the reactivity of the halogen in RX and by the reactivity of the metal. With metals that form moderately or slightly reactive RM compounds, the reaction tends to stop at the RM stage unless the RX compound is highly reactive.

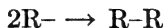
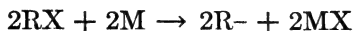


With highly reactive metals, like the alkali metals, the reaction involves only one-half the quantity of metal used above and the chief product is an R-R compound.

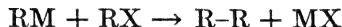
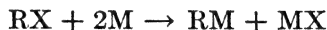


The latter reaction is known as the Wurtz-Fittig reaction, and although it is commonly associated with alkali metals it will be recalled that lithium does not react to give R-R compounds unless the RX compound be very reactive or drastic conditions be used.

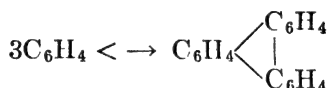
A large amount of work has been done on the mechanism of the Wurtz-Fittig reaction, and the two most widely held interpretations involve the intermediate formation of free radicals,



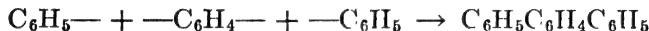
and the intermediate formation of organoalkali compounds.



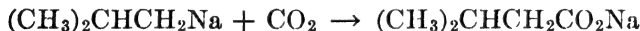
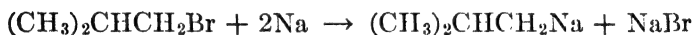
The formation of compounds like triphenylene and *o*-diphenylbenzene in the reaction mixture obtained from chlorobenzene and sodium can be quite satisfactorily explained on the basis of intermediate phenyl radicals which can disproportionate to phenylene radicals. These unite to give triphenylene,



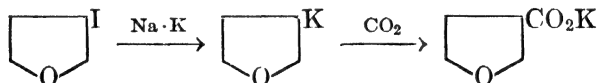
or the phenylene and phenyl radicals can combine to give *o*-diphenylbenzene.⁶³



Part of the case for the intermediate formation of RM compounds rests on the capture of such compounds during the Wurtz-Fittig reaction. For example, isovaleric acid is obtained by the action of carbon dioxide on a reaction mixture of sodium and isobutyl bromide.⁶⁴



Actually, an RM compound has been isolated in a reaction of 3-iodofuran and sodium-potassium alloy.^{65a}



The isolation of small quantities of the RK compound was attributed in part to the uncommon inertness of a β -substituted halogen in furan.

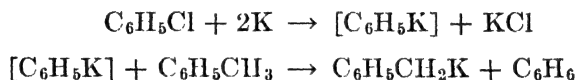
⁶³ Bachmann and Clarke, *ibid.*, **49**, 2089 (1927).

⁶⁴ Schorigin, *Ber.*, **41**, 2711 (1908); **43**, 1938 (1910); Ziegler and Schäfer, *Ann.*, **479**, 150 (1930); Hückel, Kraemer, and Thiele, *J. prakt. Chem.*, **142**, 207 (1935).

⁶⁵ (a) Gilman and Wright, *J. Am. Chem. Soc.*, **55**, 2893 (1933). (b) Bockmühl and Ehrhart, *Fr. pat.*, 736,428 [*Chem. Zentr.*, II, 2193 (1933)]. (c) Morton and Hechenbleikner, *J. Am. Chem. Soc.*, **58**, 1697, 2599 (1936). (d) Bachmann and Wiselogle, *ibid.*, **58**, 1943 (1936). (e) Gilman, Pacevitz, and Baine, *ibid.*, **62**, 1514 (1940). See, also, Morton and Massengale, *ibid.*, **62**, 120 (1940).

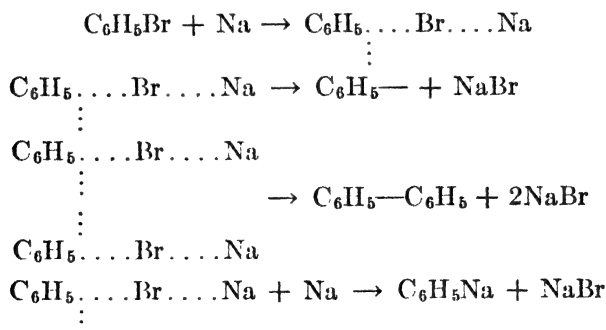
However, recent experiments have shown that organosodium compounds can be prepared directly from sodium and a variety of RX compounds. Phenylsodium is obtainable in an 89 per cent yield from chlorobenzene in benzene; ^{65b,c} amyl chloride gives amylsodium and amylidene disodium ($\text{C}_5\text{H}_{10}\text{Na}_2$), which on carbonation form caproic and butylmalonic acids, respectively, in a combined yield of 56 per cent; ^{65c} and triphenylchloromethane in ether and benzene reacts rapidly with sodium, provided that fresh surfaces of the metal are exposed throughout the reaction, to give a 96 per cent yield of triphenylmethylsodium. ^{65d}

Even phenylpotassium appears to be formed transitorily in a reaction between chlorobenzene and potassium in the presence of toluene. What probably occurs is lateral metalation of toluene by the intermediately formed phenylpotassium to yield benzyipotassium in 84 per cent yield. ^{65e}



What appears to be a related metalation is the transition from an initial 80 per cent yield of *p*-tolylsodium from *p*-chlorotoluene and sodium in toluene at 35°, to a 79 per cent yield of benzyilsodium when the mixture is refluxed. ^{65e}

It is probable that both free radicals and RM compounds are involved in the reaction. Furthermore, it seems reasonable that another somewhat unusual reaction precedes the intermediate formation of free radicals and RM compounds. It has been shown that RX compounds are carriers of alkali metals as a consequence of the possible prior formation of complexes designated as "metal halyls," by analogy with metal ketyls. These halyls can lose MX to give a free radical or R-R compound, or react with more metal to give an RM compound. ⁶⁶



⁶⁶ Morton and Stevens, *J. Am. Chem. Soc.*, **54**, 1919 (1932). For other recent studies on mechanisms of the Wurtz-Fittig reaction see the following: Whitmore, Popkin, Bernstein, and Wilkins, *ibid.*, **63**, 124 (1941); Gilman and Moore, *ibid.*, **62**, 1843 (1940); Blum-Bergmann, *ibid.*, **60**, 1999 (1938); Richards, *Trans. Faraday Soc.*, **36**, 956 (1940); Whitmore and Zook, *J. Am. Chem. Soc.*, **64**, 1783 (1942).

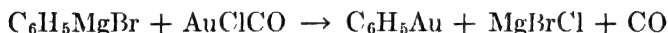
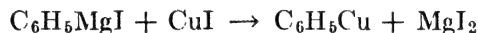
If it be granted that RM formation is, to some extent, an intermediate stage in coupling reactions to give R-R compounds, then it may be concluded that all metals have formed or will form RM compounds inasmuch as metals generally react with RX compounds to give R-R compounds. Sometimes the relatively drastic conditions necessary to effect such coupling are just those which involve pyrolysis of the thermally labile types.



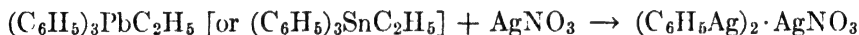
GROUP I. B-FAMILY

[Cu, Ag, Au]

The Grignard reagent has been used for the preparation of organo-copper,^{67,68} organosilver,^{67,68,69} and organogold⁷⁰ compounds.



A mixed compound of phenylsilver and silver nitrate has been obtained as follows:⁷¹



This reaction illustrates the greater reactivity of unsymmetrical organometallic compounds, inasmuch as the symmetrical R_4Pb and R_4Sn compounds do not react with silver nitrate.

The insoluble organocopper and organosilver compounds react in a normal manner with the more reactive functional groups. For example, the phenyl derivatives with acid chlorides give ketones; with allyl bromide they give allylbenzene; and with phenyl isocyanate, benzanilide. The organocopper compounds are more reactive, both on the basis of yields of products and the wider variety of functional groups with which they enter into reaction. However, neither the copper nor the silver compounds react with benzonitrile. Because of the high instability of RAu compounds no study has been made of this type with organic compounds having functional groups.

⁶⁷ Reich, *Compt. rend.*, **177**, 322 (1923).

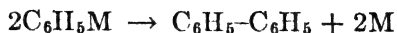
⁶⁸ Gilman and Straley, *Rec. trav. chim.*, **55**, 821 (1936).

⁶⁹ Krause and Wendt, *Ber.*, **56**, 2064 (1923).

⁷⁰ Kharasch and Isbell, *J. Am. Chem. Soc.*, **52**, 2919 (1930); for recent investigations on the chemistry of organic compounds of gold see Gibson, *Brit. Assoc. Advancement Sci. Rept.*, 35 (1938) [*C. A.*, **33**, 2838 (1939)].

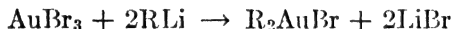
⁷¹ Krause and Schmitz, *Ber.*, **52**, 2150 (1919).

The most characteristic reaction of the univalent copper, silver, and gold compounds is the prompt and complete decomposition to R-R compound and metal.

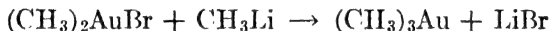


With a selected R group, the order of decreasing thermal stability is: RCu, RAg, RAu. This is apparently just the opposite of the order of increasing relative reactivities toward common functional groups. Some of the compounds decompose explosively, and rubbing of a very small sample of dry phenylsilver results in a violent detonation.

There are three other types of organogold compounds: $RAuX_2$, R_2AuX , and R_3Au . Of these, the R_2AuX compounds are most stable;^{70, 72} they are generally best prepared in ether by the following reaction.



The R_3Au types can be prepared in ether at very low temperatures.



The thermally labile trimethylgold can be stabilized by forming a complex with ethylenediamine or with α -aminopyridine. As general rules, arylmetallic compounds are more stable than alkylmetallic compounds, and methylmetallic compounds are more thermally stable than other alkyl types.

The high instability of the copper, silver, and gold compounds may account for some transformations. First, a satisfactory procedure for the formation of R-R compounds is to treat an $RMgX$ compound with copper or silver salts.⁷³ Undoubtedly, in such reactions the RM compound is first formed and then decomposes to R-R and metal. Second, small quantities of copper halides accelerate reaction of the Grignard reagent with RX compounds⁷⁴ and with nitriles.⁷⁵ It is possible that in such reactions the thermolabile organocopper compounds decompose to copper and free radicals, and that the latter may function catalytically by setting up chain reactions.^{68, 76a} Thermal decompo-

⁷² Brain and Gibson, *J. Chem. Soc.*, 762 (1939).

⁷³ Gardner and Borgstrom, *J. Am. Chem. Soc.*, **51**, 3375 (1929); Gilman and Parker, *ibid.*, **46**, 2823 (1924); Danehy and Nieuwland, *ibid.*, **58**, 1609 (1936); Joseph and Gardner, *J. Org. Chem.*, **5**, 61 (1940).

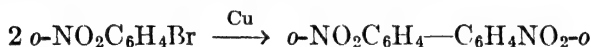
⁷⁴ Danehy, Killian, and Nieuwland, *J. Am. Chem. Soc.*, **58**, 611 (1936); Linn and Noller, *ibid.*, **58**, 816 (1936).

⁷⁵ Gilman, St. John, St. John, and Lichtenwalter, *Rec. trav. chim.*, **55**, 577 (1936).

⁷⁶ (a) Kharasch and co-workers, *J. Am. Chem. Soc.*, **63**, 2305, 2308, 2315, 2316 (1941).

(b) Bickley and Gardner, *J. Org. Chem.*, **5**, 126 (1940); Gilman and Jones, *J. Am. Chem. Soc.*, **62**, 2357 (1940).

sition of RM compounds in the presence of a solvent is not a simple reaction, and it may or may not involve free radicals.^{76b} Catalytic quantities of some metallic halides like cuprous chloride have recently been shown by Kharasch and co-workers^{76a} to exert a pronounced effect on the course of some Grignard reactions. Third, the inability of free radicals to pick up gold mirrors may be due to the uncommon thermal instability of organogold compounds. An ingenious indirect application of this idea was used in some free-radical studies. Neither methyl nor ethyl radicals would pick up beryllium deposited on quartz, possibly because of the beryllium reacting with the quartz. Accordingly, beryllium was first deposited on gold and then dimethylberyllium and diethylberyllium were formed from methyl and ethyl radicals, respectively.⁷⁷ Fourth, there is a possibility that organocopper compounds are intermediates in the Ullmann⁷⁸ reaction, which involves coupling by heating an aryl halogen compound with copper.



From such a viewpoint the Ullmann reaction may be related to the Wurtz-Fittig reaction. The syntheses of diaryl amines and diaryl ethers from reaction of aryl halides with aryl amines and with salts of phenols, respectively, do not involve intermediate organocopper compounds.^{79a}

It is probable that organometallic compounds are formed transiently when metals are used as catalysts in the decomposition of RM compounds to R-R compounds. The decreasing order of effectiveness of some metals in converting diphenylmercury to diphenyl is: Pd, Pt, Ag, Au, Co, Cu, Fe, Zn; and the decreasing order for the decomposition of dibenzylmercury is: Pd, Pt, Ag, Au, Cu, Zn, Fe, Co.^{79b}

Photochemical Activation. Light has a marked accelerating effect on the rate of preparation of phenylsilver from phenylmagnesium bromide and silver bromide. Perhaps the first example of photochemical activation in the preparation of RM compounds was Frankland's⁸⁰ study of the reaction of tin and ethyl iodide. It is known that light also accelerates the formation of some organomercury compounds: methylmercuric iodide from methyl iodide and mercury, and benzylmercuric iodide from benzyl iodide and mercury. Also, ultra-violet light accelerates the formation of some organomagnesium iodides. The mechanism of activation in these and other preparations of RM compounds may

⁷⁷ Paneth and Loleit, *J. Chem. Soc.*, 366 (1935).

⁷⁸ Ullmann and co-workers, *Ber.*, **34**, 2174, 3802 (1901).

⁷⁹ (a) Weston and Adkins, *J. Am. Chem. Soc.*, **50**, 859 (1928). (b) Rasuvaev and Koton, *Ber.*, **66**, 854 (1933); Koton, *Ber.*, **66**, 1213 (1933). See, also, Hodgson and Elliott, *J. Chem. Soc.*, 123 (1937).

⁸⁰ Frankland, *Ann.*, **85**, 329 (1853).

not be alike. With organomercurials, there may be first a photochemical decomposition of mercurous iodide: $\text{Hg}_2\text{I}_2 \rightarrow \text{Hg} + \text{HgI}_2$. Then the very finely divided mercury acts upon the RI compound to give RHgI .⁸¹ Apparently, the organic *iodides* are most responsive to photochemical activations concerned with the preparation of organometallic compounds.

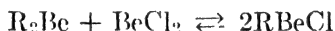
GROUP II. A-FAMILY

[Be, Mg, Ca, Sr, Ba, Ra]

Organoberyllium compounds are best prepared from beryllium chloride and the Grignard reagent.



Dimethylberyllium crystallizes in white needles, and the low-molecular-weight dialkylberyllium compounds are volatile and inflammable. The R_2Be compounds and beryllium chloride give RBeCl , and an equilibrium like that with Grignard reagents is established.



In general, the organoberyllium compounds show the reactions of Grignard reagents, but at a slower rate.⁸²

Organoberyllium and organomagnesium compounds are best set apart from the other RM compounds derived from alkaline-earth metals. For example, the organocalcium compounds not only react more readily than the corresponding RMgX compounds but also they occasionally show different reactions. A significantly different reaction is observed with some conjugated systems. As a rule, organoberyllium compounds and Grignard reagents add 1,4 to the conjugated system in a compound like benzalacetophenone.^{29a, 83} Organocalcium compounds add 1,2 to the carbonyl linkage (p. 511).

The 1,2-addition to the carbonyl group of a conjugated system is characteristic of the more reactive RM types like the organolithium compounds. It is not surprising, therefore, to observe that, although phenylmagnesium bromide adds 1,4 to the lateral-nuclear conjugated system in benzophenone-anil, phenyllithium, -sodium, -potassium, and phenylcalcium iodide add 1,2 to give triphenylmethylaniline.^{29a}



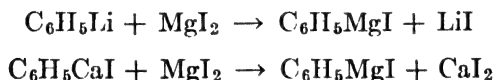
⁸¹ Maynard, *J. Am. Chem. Soc.*, **54**, 2108 (1932).

⁸² Gilman and Schulze, *ibid.*, **49**, 2904 (1927); *J. Chem. Soc.*, 2663 (1927).

⁸³ A particularly interesting exception is described by Smith and Hanson, *J. Am. Chem. Soc.*, **57**, 1326 (1935); Stevens, *ibid.*, **57**, 1112 (1935).

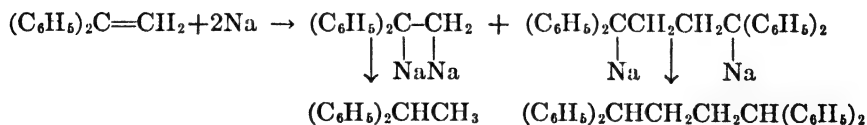
This is one of several illustrations which warrant the consideration of organocalcium compounds with the organoalkali compounds rather than with the Grignard reagents.⁸⁴ Another is the reaction with azobenzene.^{29b} (p. 512).

Incidentally, the definitely unlike type of addition of organolithium and -calcium compounds to conjugated systems makes it possible to establish the interchange of metals in some RM reactions. For example, it has been postulated that a less reactive RM compound can be prepared from a more reactive RM compound and the halide of a metal which can form a less reactive organometallic compound. On such a basis one would expect the following transformations.



There is no convenient way for isolating the phenylmagnesium iodide from such reactions. However, isolation is not necessary if the phenylmagnesium iodide can be definitely characterized. The reaction of the resulting mixtures with benzalacetophenone provides a means for establishing the formation of phenylmagnesium iodide. When benzalacetophenone is added to either reaction mixture only the 1,4-addition product is isolated, and none of the 1,2-addition product characteristic of RLi and RCaI compounds is obtained. Recently,^{8c} color test II has been used to establish the conversion of phenyllithium to phenylmagnesium iodide by means of magnesium iodide.

Relatively little work has been reported on organostrontium and organobarium compounds. However, from available information these RM types are of a relatively high order of reactivity which warrants their consideration with organoalkali compounds rather than with Grignard reagents. It is possible to arrive at their probable reactivities by an indirect procedure. 1,1-Diphenylethylene adds alkali metals in liquid ammonia to give organoalkali compounds which when hydrolyzed yield 1,1-diphenylethane and 1,1,4,4-tetraphenylbutane.⁸⁵



In general, it may be stated that where there is a 1,4-addition or a dimerizing addition of a metal to 1,1-diphenylethylene to give 1,1,4,4-tetraphenylbutane an RM compound of that metal will add to an

⁸⁴ Gilman, Kirby, Lichtenwalter, and Young, *Rec. trav. chim.*, **55**, 79 (1936).

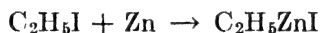
⁸⁵ Wooster and Ryan, *J. Am. Chem. Soc.*, **56**, 1133 (1934).

olefinic linkage. This is definitely true of organoalkali compounds like those of lithium and sodium. Under corresponding conditions, calcium, strontium, and barium behave like lithium and sodium toward 1,1-diphenylethylene in liquid ammonia. From this one may conclude that RM compounds of calcium, strontium, and barium are sufficiently reactive to add to an olefinic linkage.⁸⁶

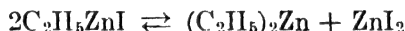
GROUP II. B-FAMILY

[Zn, Cd, Hg]

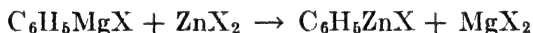
Zinc. Alkylzinc compounds were the first organometallic compounds prepared. Their synthesis is readily effected by the action of zinc on an alkyl iodide or on a mixture of alkyl iodide and bromide.⁸⁷



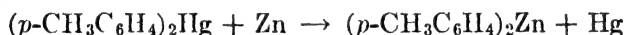
The alkylzinc halides when heated give the R_2Zn compound,



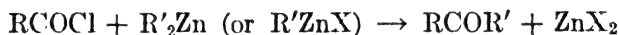
and the reaction can be reversed. The arylzinc halides are best prepared from the Grignard reagent,



and the diarylzinc compounds from the mercurials.⁸⁸

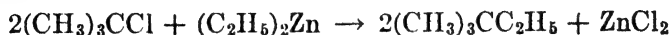


For a long time, the organozinc compounds were used extensively for the synthesis of other RM compounds and for the preparation of ketones from acid chlorides,



particularly by Blaise and co-workers.⁸⁹ Latterly, however, they have been largely superseded by other organometallies, particularly by the Grignard reagents and organocadmium compounds. This has been due to the ease of preparation and manipulation of other RM compounds which are less inflammable and give better yields of products.

Perhaps the only two present significant applications of the organozinc compounds are reaction with tertiary halides,⁸⁷



⁸⁶ Gilman and Bailie, *J. Org. Chem.*, **2**, 84 (1937).

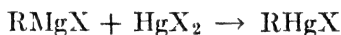
⁸⁷ Noller, *J. Am. Chem. Soc.*, **51**, 594 (1929).

⁸⁸ Kocheshkov, Nesmeyanov, and Potrosov, *Ber.*, **67**, 1138 (1934).

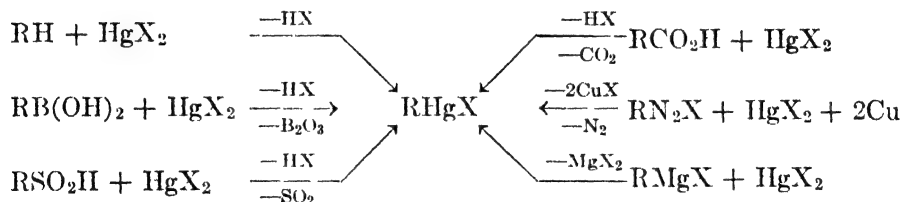
⁸⁹ Blaise, *Bull. soc. chim.*, [4] **9**, 1-XXVI (1911).

This relatively slow rate of addition of diethylcadmium to the carbonyl linkage indicates that organocadmium compounds might react satisfactorily with acid chlorides to give ketones, and that reaction would be arrested at ketone formation. Actually this happens, and organocadmium compounds are now some of the reagents of choice for the formation of ketones from an acid chloride or an acid anhydride and an RM compound.^{35, 92b}

Mercury. The history of organozinc and organomercury compounds reveals in a striking manner how the emphasis on particular organometallic types has shifted. The zinc and mercury compounds were not only among the first organometallic compounds to be discovered, but they were early developed in so successful a manner that for a long time they dominated the field of organometallic compounds. Their extensive applications as tools for syntheses included the preparation from them of many other RM compounds. Today, they not only have a highly restricted use for the preparation of other organometallic compounds, but are actually best prepared, generally, by means of other RM compounds, particularly the Grignard reagents.



There are numerous methods for the preparation of mercurials, and, in general, they can be formed wherever an easily replaced hydrogen atom is available or where a group is readily replaced by a hydrogen atom.

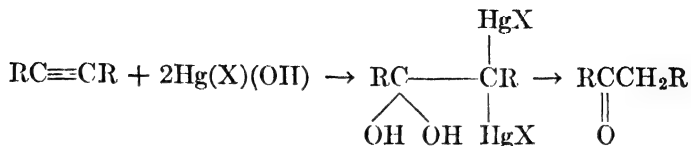
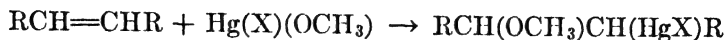


Obviously, since organomercurials are cleaved by mineral acids the latter must be removed in order to effect reaction.

Incidentally, the several methods for the preparation of organomercurials illustrate an application of mercurials as derivatives for the characterization of less stable or less definitive types. A more restricted application of mercurials as derivatives depends on the addition of a basic mercuric salt to ethylenes and acetylenes.^{93a} This reaction may

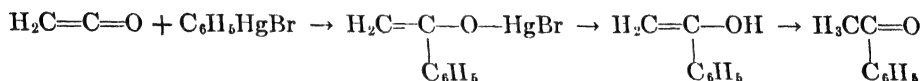
⁹³ (a) Wright, *J. Am. Chem. Soc.*, **57**, 1993 (1935); Nesmeyanov and Freidlina, *Ber.*, **69**, 1631 (1936). See, also, Connor and Van Campen, *J. Am. Chem. Soc.*, **58**, 1131 (1936), for the use of mercuric chloride in a general test for methylene compounds. (b) Brown and Wright, *ibid.*, **62**, 1991 (1940).

be of possible diagnostic value in differentiating *cis* and *trans* isomers by the rates of formation of some mercurials.^{93b}



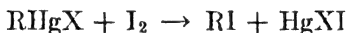
The reaction with acetylenes is exemplified by the industrial conversion of acetylene to acetaldehyde.

Organomercurials are the least active organometallic compounds in the first two groups, and this is reflected in the fact that they are the only organometallics in the first two groups which can be manipulated in water and other hydroxylated solvents. The only unsaturated functional group to which they add after the manner of reactive RM types is the carbonyl group in a highly reactive compound like ketene or, very slowly, with Michler's ketone.

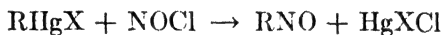


The same reaction, of course, occurs with organozinc and organocadmium compounds, the organozinc compounds reacting most smoothly to give the highest yields of methyl ketones.⁹⁴ As a rule, ketones are formed with difficulty from mercurials and acid halides, which is in sharp contrast with the related reactions of the zinc and cadmium compounds. Likewise, RX compounds undergo highly restricted metathetical reactions with organomercury compounds.

However, the halogens (particularly iodine) react smoothly.⁹⁵



Also, the nitro and nitroso groups can be introduced.^{96a}



A related reaction, in which nitroso compounds may be intermediates, is the formation of diazonium nitrates by interaction of N_2O_3 and N_2O_4 with R_2Hg and a variety of other RM compounds.^{96b} These are some of the more important replacement reactions of arylmercurials.

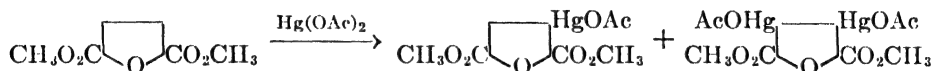
⁹⁴ Hurd, Jones, and Blunck, *J. Am. Chem. Soc.*, **57**, 2033 (1935). Hurd and Roe, *ibid.*, **61**, 3355 (1939), observed no reaction between ketene and tetraethyllead.

⁹⁵ Whitmore and Thorpe, *ibid.*, **55**, 782 (1933). See, also, Whitmore, "Organic Compounds of Mercury," Chemical Catalog Co., New York (1921), pp. 67-73.

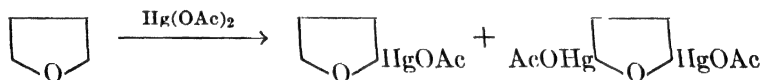
⁹⁶ (a) Smith and Taylor, *J. Am. Chem. Soc.*, **57**, 2460 (1935). (b) Makarova and Nesmeyanov, *J. Gen. Chem. (U.S.S.R.)*, **9**, 771 (1939) [*C. A.*, **34**, 391 (1940)].

Some other reactions of mercurials have already been considered, like the preparation of organoalkali compounds and the cleavage of unsymmetrical mercurials by acids.

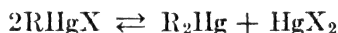
Inasmuch as mercuration of aromatic nuclei is not only a relatively mild reaction compared with nitration and bromination, but also leads sometimes to substitution in otherwise inaccessible positions, mercuration finds itself peculiarly adapted for many aromatic syntheses. A striking illustration of the relative ease of mercuration is found with dimethyl furan-2,5-dicarboxylate. This compound is inordinately resistant to typical nuclear substitution reactions like nitration, sulfonation, bromination, and the Friedel-Crafts reaction; however, mercuration replaces β -hydrogens.



Inasmuch as α -hydrogens in furan undergo prompt and smooth nuclear substitution reactions it is not surprising to find that furan is mercured almost instantaneously at room temperature.



The general equilibrium between mixed and simple organometallic compounds is observable with mercurials.



Any reagent which removes mercuric salt from the zone of reaction will shift the equilibrium to the right, and this is accomplished chiefly by reducing agents such as sodium, stannous chloride, sodium thiosulfate, and hydrazine.

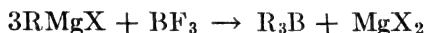
In the Zn-Cd-Hg series, the thermal stabilities of the organometallies apparently decrease with increase in atomic weight, as in the adjoining Cu-Ag-Au series in the B-Family of Group I. However, the order is reversed with reactions like oxidation and cleavage by active hydrogen compounds: the organozinc compounds are most inflammable and most readily cleaved by water or other reagents having acidic hydrogens. The high inflammability of organozincs and the high toxicity of organomercurials have necessitated special manipulative procedures which, in turn, have encouraged the greater development of other organometallies. However, it should be emphasized that convenience in manipulation may be secondary in importance to inherent differences in chemical reactivity which warrant the use of one RM type rather than another. We need only recall that the highly reactive organoalkali

compounds were extensively developed despite the early need of special apparatus and technique. The matter of toxicity is also to be weighed against other properties. Numerous RM types are toxic, and, although mercurials are more toxic than many other RM compounds, it is possible by the proper introduction of substituents to get mercurials of high therapeutic value.

GROUP III. A-FAMILY

[B, Al, Sc, Y, La, Ac]

Boron. The trialkyl- and triarylboron compounds are best prepared from boron trifluoride and the Grignard reagent.⁹⁷



It has been shown recently that the R_3B compounds actually undergo typical organometallic addition reactions to the carbonyl group in such compounds as benzaldehyde and phenyl isocyanate.⁹⁸ This suggests that boron partakes more of the nature of a metal than a metalloid, and is corroboratory evidence for the metallicity of boron. However, such addition reactions are slow, and direct comparisons with related zinc and aluminum compounds show that the order of relative reactivities is:



In such reactions, only two of the R groups are involved under customary conditions, and one of the products is a monosubstituted boric acid, $\text{RB}(\text{OH})_2$. These organic boric acids are quite stable, and actually phenylboric acid can be nitrated by means of fuming nitric acid to give the three isomeric nitrophenylboric acids $[\text{NO}_2(\text{C}_6\text{H}_4\text{B}(\text{OH})_2)]$, without any significant cleavage of the phenyl-boron linkage.⁹⁹

The disubstituted boric acids, R_2BOH , which are solids like the monosubstituted boric acids, indicate the relative inertness of organoboron compounds, for here, too, a given molecule contains not only the organometallic linkage (carbon-boron) but also the active hydrogen present in the hydroxyl group. In general, it appears that organoboron compounds may be anomalous with respect to cleavage by active or acidic hydrogen, for the simple trialkylboron compounds are spontaneously inflammable and yet uncommonly resistant to the action of water

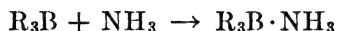
⁹⁷ Krause and Nitsche, *Ber.*, **55**, 1261 (1922).

⁹⁸ Gilman and Marple, *Rec. trav. chim.*, **55**, 76, 133 (1936).

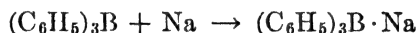
⁹⁹ Seaman and Johnson, *J. Am. Chem. Soc.*, **53**, 711 (1931); Ainley and Challenger *J. Chem. Soc.*, 2171 (1930). See, also, Bettman, Branch, and Yabroff, *J. Am. Chem. Soc.* **56**, 1865 (1934), for the dissociation constants of substituted phenylboric acids.

and alcohol. Trimethylboron is the only known gaseous organometallic compound.

Trialkylboron and triarylboron compounds form addition compounds with nitrogen bases like ammonia and a wide variety of amines to give ammines.



A related reaction is observed with sodium.



and on the basis of this and other evidence it has been suggested that triarylboron compounds might be considered as free radicals, analogous to triarylmethyls. Both triphenylboron and triphenylmethyl add sodium from dilute amalgam, and in both cases the sodium is removed by mercury.¹⁰⁰ Tri- α -naphthylboron adds two atoms of sodium, and the second atom is held much less firmly than the first.

Aluminum. Trialkylaluminum compounds are prepared from aluminum chloride and the Grignard reagent; and triarylaluminum compounds from aluminum and the mercurials. The mixed organoaluminum compounds are conveniently prepared by direct interaction of aluminum with some RX compounds.^{101a}



The organoaluminum compounds either fume or are spontaneously inflammable. They undergo many of the reactions of Grignard reagents, but at a slower rate. Like the corresponding boron and zinc compounds they react with typical functional groups at rates which place the functional groups in an order of relative reactivities like that established with Grignard reagents: $-\text{CHO} > -\text{COC}_6\text{H}_5 > -\text{C}\equiv\text{N}$.^{101b}

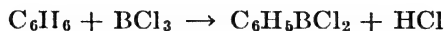
However, mixed organoaluminum etherates react with ketones to give highly condensed products. This raises a question concerning the intermediate formation of organoaluminum compounds in the Friedel-Crafts reaction. It was originally suggested by Friedel and Crafts that the reactions which later came to bear their name proceed by way of organoaluminum compounds.^{102a} It is possible, under drastic condi-

¹⁰⁰ Bent and Dorfman, *J. Am. Chem. Soc.*, **57**, 1259 (1935); Krause and co-workers, *Ber.*, **59**, 777 (1926); *Ber.*, **63**, 2347 (1930).

¹⁰¹ (a) Hnizda and Kraus, *J. Am. Chem. Soc.*, **60**, 2276 (1938); Gilman and Apperson, *J. Org. Chem.*, **4**, 162 (1939); Grosse and Mavity, *ibid.*, **5**, 106 (1939). (b) Gilman and Marple, *Rec. trav. chim.*, **55**, 133 (1936).

¹⁰² (a) Friedel and Crafts, *Ann. chim. phys.*, [6] **14**, 433 (1888). (b) Pace, *Atti accad. Lincei*, **10**, 193 (1929) [*C. A.*, **24**, 1360 (1930)].

tions, to effect the following reaction between boron trichloride and benzene.^{102b}



However, even if it be granted that the related aluminum chloride will react in an analogous manner and under the relatively moderate conditions existing in a Friedel-Crafts reaction, it is still necessary to consider the relative reactivities of mixed compounds like RAlCl_2 and R_2AlCl . Confining attention to the two most important Friedel-Crafts reactions, ketone formation and alkylation, present evidence is inadequate to rule out the participation of intermediate organoaluminum compounds *if* such organometallic compounds are formed. Complexes between ketones and aluminum chloride do not give condensation products when treated with organoaluminum halides under moderate conditions, and the ketones are recovered upon hydrolysis. Furthermore, highly satisfactory yields of ketones and keto acids are obtained by interaction of ether-free organoaluminum halides with acid chlorides or acid anhydrides.

In alkylation reactions, etherates of phenylaluminum iodides and alkyl iodides yield small quantities of homologs of benzene together with large amounts of resins.¹⁰³ However, when ether-free organoaluminum halides are used, the homologs of benzene are obtained in satisfactory yields with no resin formation.

Scandium, Yttrium, and Lanthanum. Triethylscandium and triethylyttrium have been prepared from the metallic chlorides and ethylmagnesium bromide. These organometallic compounds have been described as liquids which oxidize readily and are decomposed promptly by water.¹⁰⁴

Free alkyl radicals have been shown¹⁰⁵ to react readily with lanthanum by the Paneth technique. This indicates that a compound like trimethyl lanthanum may have been prepared, even though there is no present information concerning its properties.

¹⁰³ Leone and co-workers, *Gazz. chim. ital.*, **55**, 294, 301, 306 (1925).

¹⁰⁴ Plets, *Compt. rend. acad. sci. U.R.S.S.*, **20**, 27 (1938) [*C. A.*, **33**, 2105 (1939)].

¹⁰⁵ Rice and Rice, "The Aliphatic Free Radicals," The Johns Hopkins Press, Baltimore (1935), p. 58.

GROUP III. B-FAMILY

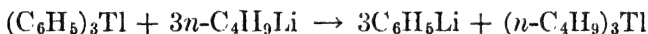
[Ga, In, Tl]

The R_3M types of gallium,¹⁰⁶ indium,¹⁰⁷ and thallium¹⁰⁸ are generally prepared by reaction of the metal with a mercurial or by interaction of the halide salt with $RMgX$ or RLi compounds.

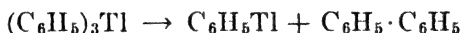
In general, these compounds are of moderate reactivity, but less reactive than the Grignard reagent. For example, they react with benzaldehyde, benzalacetophenone, and benzoyl chloride, but not with benzonitrile. As evidence of their moderate reactivity they undergo 1,4-addition, but no 1,2-addition, with benzalacetophenone (p. 511). Also like other moderately reactive RM compounds, they react more promptly with benzoyl chloride than with benzophenone (p. 501). Although only one phenyl group in triphenylthallium reacts under customary conditions, all three groups in R_3Ga and R_3In compounds are involved with some reactants. In this latter connection it is of interest that diphenylindium iodide and phenylindium diiodide react with benzoyl chloride.^{107a}

The following order of decreasing reactivities has been established: ^{106a}, ^{107a}, ^{108a} R_3In , R_3Ga , R_3Tl .

Three incidental reactions are noteworthy. First, both triphenylthallium and diphenylthallium bromide react with metallic mercury to give diphenylmercury.^{108a} These metal-replacement reactions, which are probably equilibria, are interesting because of the ready formation of a less reactive RM' compound (diphenylmercury) from an RM compound and a metal. Second, a prompt metal-metal interconversion occurs between triphenylthallium and *n*-butyllithium.¹⁰⁹



Third, triphenylthallium is converted in a boiling xylene solution to phenylthallium and biphenyl.¹⁰⁹



This phenylthallium is actually more reactive than triphenylindium and decidedly more reactive than triphenylthallium, but less reactive

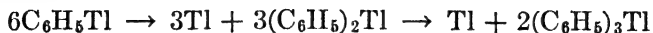
¹⁰⁶ (a) Gilman and Jones, *J. Am. Chem. Soc.*, **62**, 980 (1940). (b) Dennis and Patnode, *ibid.*, **54**, 182 (1932); Kraus and Toonder, *ibid.*, **55**, 3547 (1933); Renwanz, *Ber.*, **65**, 1308 (1932).

¹⁰⁷ (a) Gilman and Jones, *J. Am. Chem. Soc.*, **62**, 2353 (1940). (b) Dennis, Work, Rochow, and Chamot, *ibid.*, **56**, 1047 (1934); Schumb and Crane, *ibid.*, **60**, 306 (1938).

¹⁰⁸ (a) Gilman and Jones, *ibid.*, **61**, 1513 (1939). (b) Groll, *ibid.*, **52**, 2998 (1930) Menzies and Cope, *J. Chem. Soc.*, 2862 (1932); Birch, *ibid.*, 1132 (1934).

¹⁰⁹ Gilman and Jones, *J. Am. Chem. Soc.*, **62**, 2357 (1940).

than a Grignard reagent like phenylmagnesium bromide. In the absence of a reactant, the transitorily formed phenylthallium is readily converted to triphenylthallium and metallic thallium, probably by way of diphenylthallium.



Coördination Compounds (p. 1879). Organogallium compounds are peculiarly appropriate for illustrating some effects of coördination compounds in organometallic chemistry. The simple triethylgallium $[(\text{C}_2\text{H}_5)_3\text{Ga}]$ reacts violently with water; the etherate $[(\text{C}_2\text{H}_5)_3\text{Ga} \cdot (\text{C}_2\text{H}_5)_2\text{O}]$ vigorously; and the ammine $[(\text{C}_2\text{H}_5)_3\text{Ga} \cdot \text{NH}_3]$ only very slowly.^{106b}

Triphenylgallium only gives a Michler's ketone color test when an excess of the RM compound is heated in a benzene solution with the ketone. The color which develops is much weaker than that observed with the related triphenylthallium, which is less prone to form coördinate linkages.

Varying coördination effects of solvents may influence profoundly the relative reactivities of RM compounds. For example, an ether solution of Michler's ketone with one equivalent of phenylmagnesium bromide regenerates most of the ketone on hydrolysis.^{110a, b} However, when benzene is used as the medium, there is less tendency for coördination formation, and addition to the carbonyl group to give a carbinol is pronounced. Phenyllithium, which is distinctly more reactive than phenylmagnesium bromide, has very little tendency to form coördination linkages. Actually, phenyllithium reacts promptly with Michler's ketone, in either benzene or ether, and none of the ketone is recovered on hydrolysis.

Several broad generalizations can be made concerning coördination compounds in organometallic chemistry. First, the slow reaction or the essential absence of reaction between some carbonyl-containing compounds (like ketones and esters) and moderately reactive RM compounds is due in part to the formation of coördination compounds. Second, the less reactive RM compounds have a generally greater tendency to form coördinate compounds. Third, the variations in the order of reactivities of some functional groups (p. 501) with different RM compounds may find an explanation in the varying stabilities of coördination compounds. Fourth, the generally greater reducing action of moderately and less active RM compounds may be due, in part,

¹¹⁰ (a) Gilman and Jones, *ibid.*, **62**, 1243 (1940); **63**, 1162 (1941). (b) Pfeiffer and Blank, *J. prakt. Chem.*, **153**, 242 (1939). See, also, Shriner and Sharp, *J. Org. Chem.*, **4**, 575 (1939).

to the greater tendency of such compounds to form coördinate linkages. Fifth, solvents can markedly influence RM reactions as a consequence of varying coördination tendencies.

GROUP IV. A-FAMILY

[Ti, Zr, Hf, Th]

Numerous attempts have been made to prepare organotitanium and organozirconium compounds, but without unequivocal success.¹¹¹ Titanium and zirconium chlorides are reduced to lower halides, and possibly to the metals, in reactions with RMgX and RLi compounds. In these reactions, the R groups may couple; disproportionate to give R + H and R—H compounds; or abstract hydrogen from the solvent to give RH compounds. The nature of the R group has a marked influence, phenyl radicals giving predominantly biphenyl, and methyl radicals almost exclusively methane.¹⁰⁹

GROUP IV. B-FAMILY

[Ge, Sn, Pb]

Germanium. In 1871 Mendeléeff predicted that ekasilicon (germanium) would form volatile organometallic compounds such as the tetraethyl derivative. This was verified in 1886 by Winkler, who discovered germanium. During an interval of about forty years practically nothing was done with these organometallic compounds, but more recently the field has been enriched, particularly as a consequence of the studies by Morgan and Dennis and Kraus.

The simple organogermanium compounds are best prepared by interaction of germanium tetrachloride with either the Grignard reagents or organozinc compounds. Two special methods of preparation are noteworthy. One is direct metalation of amines which undergo facile nuclear substitution.



The other is an interesting reaction which has also been used for organotin and organolead compounds.¹¹²

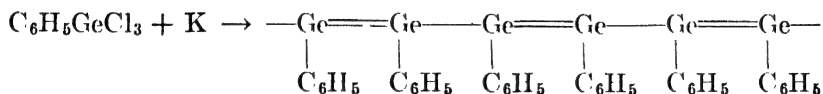


¹¹¹ Paternò and Peratoner, *Ber.*, **22**, 467 (1889); Razuvaev and Bogdanov, *J. Gen Chem. (U.S.S.R.)*, **3**, 367 (1933) [*C. A.*, **28**, 2340 (1934)]; Plets, *ibid.*, **8**, 1298 (1938) [*C. A.* **33**, 4193 (1939)].

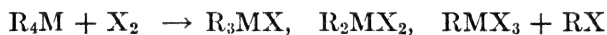
¹¹² Tchakirian and Lewinsohn, *Ann. chim.*, **12**, 415 (1939).

In this reaction, it is essential that the metal in combination with halogen does not have its maximum electrovalence and that it can in addition form a complex with alkali halides.

There is a regular gradation in properties of the compounds having R groups attached to carbon, silicon, germanium, tin, and lead. First, the thermal stabilities decrease so that organolead compounds are the least stable thermally. Second, the tendency to form large molecules with the central element joined directly to itself decreases in the same order. A compound having six germanium atoms has been prepared as follows,



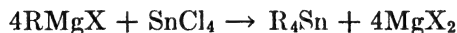
the terminal valences not being united to give hexaphenylgermanobenzene, as was supposed originally.¹¹³ Third, the tendency to form mixed hydrides like RMH_3 , R_2MH_2 , and R_3MH is lowest with the organolead compounds. Fourth, the rate of cleavage by halogens or acids is greatest with organolead compounds.



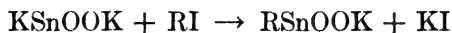
Fifth, although none of the compounds adds to a simple unsaturated linkage like the carbonyl group in aldehydes, the organometallic compounds undergo cleavage with acid halides and some reactive alkyl halides, the organolead compounds again being cleaved most readily.



Tin. The best general method for the preparation of simple organotin compounds, both aliphatic and aromatic, is the reaction between a stannic halide and the Grignard reagent.



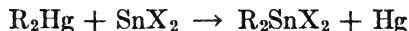
Among special methods for the preparation of organotin compounds, three are of particular interest. In the Meyer reaction, an alkylstannic acid is prepared from potassium stannite.¹¹⁴



¹¹³ Schwarz and Schmeisser, *Ber.*, **69**, 579 (1936).

¹¹⁴ Meyer, *Ber.*, **16**, 1439 (1883); Pfeiffer and Lehnardt, *Ber.*, **36**, 1054 (1903).

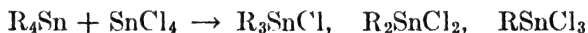
Another method is illustrated by the following reaction: ^{115a}



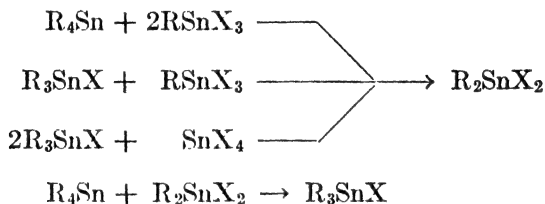
In a third procedure, the double salt of a diazonium compound with stannic chloride is treated with a finely powdered metal like copper. ^{115b}



The conversion of R_4Sn compounds to R_3SnX , R_2SnX_2 , and $RSnX_3$ types can be effected not only by halogens and halogen acids, as mentioned previously, but also by interaction with stannic halides.

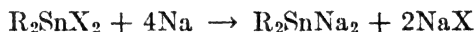


These reactions can be carried out in stages so that a 75 per cent yield of triphenyltin chloride is obtainable from tetraphenyltin and stannic chloride. Related cleavage reactions can be realized with other combinations. ^{115c}

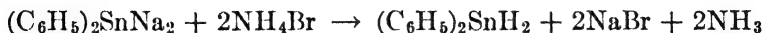


Cleavage is also effected by a variety of organic compounds containing halogen, among which are the alkyl and acyl halides mentioned earlier; ^{116a} by hydrogen; ^{79b} and by sodium in liquid ammonia. ^{116b}

The mixed organotin halides react with sodium in liquid ammonia as follows:



The sodium-tin compounds, R_2SnNa_2 and R_3SnNa , are useful synthetically, and among their many transformations is hydrolysis by ammonium chloride or bromide to give hydrides. For example, disodiumdiphenyltin gives diphenyltin dihydride. ¹¹⁷

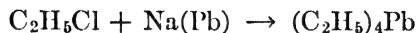


¹¹⁵ (a) Nesmeyanov and Kocheshkov, *Ber.*, **63**, 2496 (1930). (b) Kocheshkov, Nesmeyanov, and Klimova, *J. Gen. Chem. (U.S.S.R.)*, **6**, 167 (1936) [*C. A.*, **30**, 4834 (1936)]. (c) Kocheshkov, *J. Gen. Chem. (U.S.S.R.)*, **5**, 211 (1935) [*C. A.*, **29**, 5071 (1935)]; Bobashinskaya and Kocheshkov, *ibid.*, **8**, 1850 (1938) [*C. A.*, **33**, 5820 (1939)].

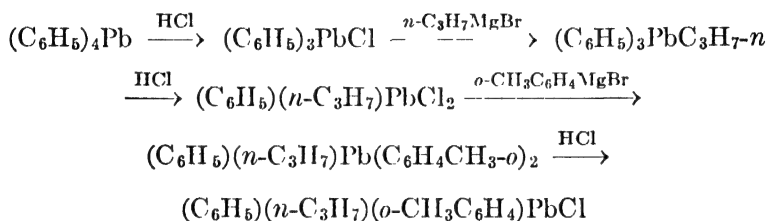
¹¹⁶ (a) Bost and Borgstrom, *J. Am. Chem. Soc.*, **51**, 1922 (1929). (b) Kraus and Sessions, *ibid.*, **47**, 2361 (1925); Kraus and Foster, *ibid.*, **49**, 457 (1927).

¹¹⁷ Chambers and Scherer, *ibid.*, **48**, 1054 (1926).

Lead. The preparation and properties of organolead compounds are very much like those of organotin compounds.¹¹⁸ Tetraethyllead, the most important organolead compound, is prepared technically, for use as an anti-knock compound, from ethyl chloride and sodium-lead alloy.

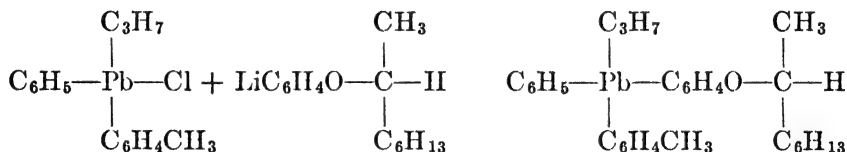


The following reactions used for the preparation of an organolead compound having four different groups attached to lead illustrate the preferential cleavage of radicals and the general procedure employed for the synthesis of a wide variety of unsymmetrical organometallic compounds¹¹⁹ (p. 424).



It will be observed that experimental conditions can be so ordered that hydrogen chloride cleaves one or two radicals, as is also true of cleavage by halogens. The order of increasing ease of cleavage of radicals is: *n*-propyl, phenyl, *o*-tolyl. Somewhat related reactions have been used for the synthesis of asymmetrical organogermanium and organotin compounds, both types being subsequently resolved to optical isomers.

No organolead compound has as yet been resolved. When the phenyl-*n*-propyl-*o*-tolyllead chloride was treated with an optically active organolithium compound,



the resulting optically active compound was an oil which could not be separated into its two diastereoisomers.

An interesting and ingenious application of radioactive organometallic compounds might be mentioned here. In quantum yield studies concerned with the photochemical decomposition or photolysis of

¹¹⁸ Calingaert, *Chem. Rev.*, **2**, 43 (1925); Gilman and Bailie, *J. Am. Chem. Soc.*, **61**, 731 (1939).

¹¹⁹ Austin, *J. Am. Chem. Soc.*, **55**, 2948 (1933). See, also, Krause and Schlöttig, *Ber.*, **58**, 427 (1925).

organolead compounds, the quantities of free radicals formed are so small that ordinary analytical methods are inadequate for their exact measurement. Accordingly, the extremely sensitive method of radioactive indicators has been employed. The metallic mirror used to capture the free methyl and ethyl radicals is a radioactive metal like radium D. Actually, the radioactive deposit is so slight as to be invisible, but it suffices to pick up the free radicals; and the newly formed alkyl-radium D compounds prepared in this manner are carried along to a cooled part of the tube (the Paneth technique) (p. 613) and measured by the usual, highly sensitive radioactive methods.^{120a}

GROUP V. A-FAMILY

[V, Cb, Ta, Pa]

There is no decisive evidence for the existence of an organometallic compound derived from a metal in the A-family of Group V. Several inorganic vanadium compounds, particularly the halides, have been treated with Grignard reagents. The general products are reduced vanadium salts, R-R compounds, and possibly some organovanadium compounds.^{120b}

Columbium pentachloride and tantalum pentachloride react with aromatic hydrocarbons, evolving hydrogen chloride and yielding intensely colored, non-crystalline compounds of the following types:^{121a}



Related compounds have been reported from reactions with vanadium tetrachloride.^{121b}

It appears likely that greater success will attend the preparation of these RM types if the Grignard reagent or other moderately reactive organometallic compounds be treated with halides in the lowest valence state. The reaction between tantalum pentachloride and RMgX or RLi compounds leads to the formation of a lower halide of tantalum and RH compounds, methane being the chief hydrocarbon when CH_3M types are used.

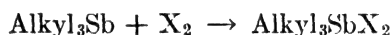
¹²⁰ (a) Leighton and Mortensen, *J. Am. Chem. Soc.*, **58**, 448 (1936); see, also, Burton, Ricci, and Davis, *ibid.*, **62**, 265 (1940). (b) Vernon, *ibid.*, **53**, 3831 (1931); Kirsanov and Sazonova, *J. Gen. Chem. (U.S.S.R.)*, **5**, 956 (1935) [*C. A.*, **30**, 1025 (1936)].

¹²¹ (a) Funk and Niederländer, *Ber.*, **61**, 1385 (1928). See Atanasyev, *Chemistry & Industry*, **59**, 631 (1940), concerning the possible formation of highly unstable phenyltantalum compounds. (b) Mertes and Fleck, *J. Ind. Eng. Chem.*, **7**, 1037 (1915).

GROUP V. B-FAMILY

[Sb, Bi]

The trialkyl and triaryl derivatives of nitrogen, phosphorus, arsenic, antimony, and bismuth show regular gradations in properties. Many of the variations in properties might have been predicted on the basis of organometallic characteristics reaching a maximum with the bismuth compounds. (1) The thermal stabilities decrease with increasing atomic weight of the central element. (2) The inflammability is greatest with the organobismuth compounds. (3) The tendency to form R_3MX_2 types by the addition of halogens decreases with descent in the family.



Actually, the trialkylbismuth compounds do not give such salts; instead one or two R groups are cleaved.

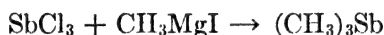


The triaryl bismuth compounds add halogens to give triarylbismuth dihalides. (4) The formation of onium compounds, by addition of an alkyl iodide, decreases generally. Trimethylantimony adds methyl iodide slowly to give tetramethylantimony iodide,

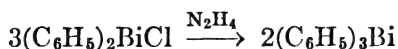
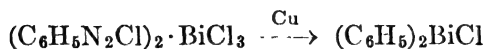
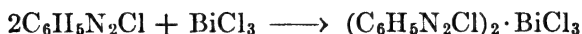


but trimethylbismuth does not add methyl iodide.^{122a}

The best general method for the preparation of trialkyl and triaryl compounds of antimony and bismuth is the reaction between a halide and the Grignard reagent.



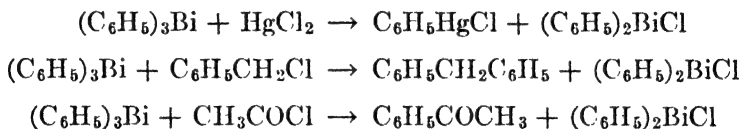
The Bart reaction^{122b} used for the preparation of arsonic acids is applicable to the stibonic acids, $\text{Aryl-SbO}_3\text{H}_2$, but not to the analogous bismuth compounds. However, it has recently been shown that organobismuth compounds can be prepared from diazonium compounds by the following typical sequence of reactions.^{122c}



¹²² (a) Davies, Norvick, and Jones, *Bull. soc. chim.*, **49**, 187 (1931). (b) Bart, *Ann.*, **429**, 55 (1922). (c) Gilman and Yablunky, *J. Am. Chem. Soc.*, **63**, 949 (1941). (d) Gilman and Yablunky, *ibid.*, **62**, 665 (1940). See Gilman and Barnett, *Rec. trav. chim.*, **55**, 563 (1936), for the use of hydrazine for converting other RMX compounds, like RHgX , to the corresponding R_2M types.

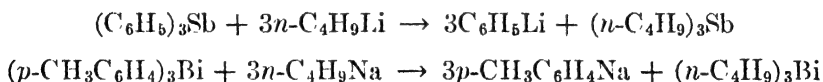
The intermediate compounds have been isolated; and hydrazine appears to be a reagent of choice for converting arylbismuth halides to triaryl-bismuth compounds.^{122d}

Studies by Challenger and co-workers, particularly with organobismuth compounds, have demonstrated that organobismuth compounds undergo more ready cleavage than organoantimony compounds. The cleavage reactions have been carried out with a wide variety of inorganic halides and some alkyl and acyl halides.^{123a}

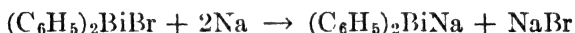


No addition of either an organoantimony or an organobismuth compound to a simple functional group like the carbonyl group in aldehydes has been reported.

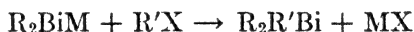
Organoantimony and organobismuth compounds undergo metal-metal interconversion reactions with organoalkali compounds.^{123b}



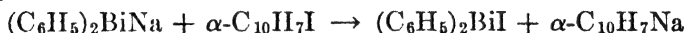
In liquid ammonia, R_2SbX and R_2BiX compounds react promptly with lithium, sodium, potassium, calcium, and barium to give deeply colored R_2SbM and R_2BiM types.^{123c}



These dimetallic compounds undergo ready reaction with RX compounds and provide one of the better procedures for the preparation of unsymmetrical organoantimony and organobismuth compounds.^{123d}



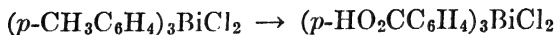
They also undergo a halogen-metal interconversion reaction in liquid ammonia.



The stability of organobismuth compounds varies markedly with the type of compound (R_3Bi , R_3BiX_2 , R_2BiX , RBiX_2), and the character and position of substituents in the R group. Among the most stable compounds are the triaryl-bismuth dichlorides, and a compound

¹²³ (a) Challenger and Ridgway, *J. Chem. Soc.*, **121**, 104 (1922). (b) Gilman, Yablunsky, and Svigoon, *J. Am. Chem. Soc.*, **61**, 1170 (1939). (c) Gilman and Yablunsky, *ibid.*, **63**, 212 (1941). (d) Gilman and Yablunsky, *ibid.*, **63**, 207 (1941). (e) Supniewski and Adams *ibid.*, **48**, 507 (1926).

like tri-*p*-tolylbismuth dichloride can be oxidized to tri-*p*-carboxyphenylbismuth dichloride by means of potassium permanganate or chromic acid.^{123c}



Extensive studies¹²⁴ of compounds like $(\text{C}_6\text{H}_5)_3\text{BiX}_2$ have shown that the order of decreasing stability of the dihalides is: R_3BiCl_2 , R_3BiBr_2 , R_3BiI_2 . However, with R_2BiX types in liquid ammonia, the order is reversed and the R_2BiI compound is most stable.^{123c}

A sensitive test, known as color test III, is characteristic not only for triarylbiomuth dihalides but also for the more reactive arylmetallic compounds like those of sodium, lithium, and magnesium.^{8c} The color test, when used for reactive arylmetallic types, is carried out readily by adding 1 cc. of the RM solution to 1 cc. of an approximately 1 per cent solution of triphenylbismuth dichloride in dry benzene. With aryl-lithium and arylmagnesium compounds a deep purple color forms instantaneously. The reaction mechanisms of this color test are as yet unknown. It is interesting that triarylarsenic dihalides and triaryl-antimony dihalides do not give the test. Using phenylmagnesium bromide, a positive test is obtainable with 1 cc. of a 0.0039 molar solution of triphenylbismuth dichloride.

GROUP VI. A-FAMILY

[Cr, Mo, W, U]

Numerous attempts have been made to prepare organometallic compounds of molybdenum, tungsten, and uranium. When the method has involved interaction of the halide salt with the Grignard reagent, the course of reaction has resembled markedly that noted with halides of the A-family of Group V: namely, reduction of the salt, coupling to form R-R compounds, and the very doubtful formation of organometallic compounds.¹²⁵ However, recent preliminary studies have shown the possibility of preparing some complex phenylmolybdenum and phenyltungsten compounds.^{126a}

The studies by Hein and co-workers^{126b} have provided a good picture of organochromium compounds. The chief reaction product of chromic

¹²⁴ Challenger and Richards, *J. Chem. Soc.*, 405 (1934).

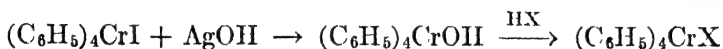
¹²⁵ Bennett and Turner, *J. Proc. Roy. Soc. N. S. Wales*, **53**, 100 (1919) [*C. A.*, **14**, 414 (1920)]; Lal and Dutt, *J. Indian Chem. Soc.*, **12**, 389 (1935) [*C. A.*, **30**, 452 (1936)].

¹²⁶ (a) Hein, *Naturwissenschaften*, **28**, 93 (1940); *Angew. Chem.*, **51**, 503 (1938). (b) Hein and co-workers, *Ber.*, **54**, 1916, 1936, 2710, 2727 (1921); *Ber.*, **57**, 8, 899 (1924); *Ber.*, **59**, 362, 751 (1926); *Ber.*, **61**, 2255 (1928); *Ber.*, **62**, 1151 (1929); *J. prakt. Chem.*, **153**, 160 (1939).

chloride and phenylmagnesium bromide is pentaphenylchromium bromide,



which with alcoholic potassium hydroxide gives pentaphenylchromium hydroxide. This strongly basic hydroxide undergoes an unusual reaction when salts are prepared from it either by the action of acids or by double decomposition with alkali salts: a phenyl group is removed and tetraphenylchromium salts result. However, tetraphenylchromium hydroxide (prepared from tetraphenylchromium iodide and silver hydroxide) behaves normally to give tetraphenylchromium salts.



Among other products of the reaction between chromic chloride and phenylmagnesium bromide are tetraphenylchromium salts and triphenylchromium salts. These, when electrolyzed in liquid ammonia, give the highly unstable, simple organochromium compounds: tetraphenylchromium, $[(\text{C}_6\text{H}_5)_4\text{Cr}]_n$, and triphenylchromium, $[(\text{C}_6\text{H}_5)_3\text{Cr}]_n$.

In color, the organochromium compounds resemble markedly the inorganic dichromates. All the organochromium compounds reported are relatively unstable thermally and quite sensitive to light and oxygen. The alkylchromium compounds appear to be particularly unstable, and none has been isolated.

Pentaphenyl-, tetraphenyl-, and triphenylchromium hydroxides are strong bases, the conductivity increasing with a decrease in the number of phenyl groups.

There is no report of the addition of an organochromium compound to an organic unsaturated grouping. Although practically nothing has been done on the possible reaction of organochromium compounds with organic compounds, it appears reasonable to expect that they will react with some alkyl and acyl halides after the manner of organotin compounds.

GROUP VI. B-FAMILY

[Po]

No study has been reported on organopolonium compounds. Polonium hydride, however, has been found to be less stable than bismuth hydride.¹²⁷ One may predict that organopolonium compounds will be found to be less stable than organobismuth compounds. Superimposed on such thermal instability will be the relatively short half-life period of the radioactive compound.

¹²⁷ Paneth and Johannsen, *Ber.*, **55**, 2622 (1922).

GROUP VII

[Mn, Ma, Re]

Organomanganese compounds, prepared by interaction of manganous iodide with Grignard reagents or organolithium compounds, are inflammable and of moderate thermal stability. They are promptly decomposed by water, yielding the parent RH compound, and they react with the usual organic functional groups at a rate somewhat like that observed with organoaluminum compounds. Accordingly, they are the most reactive of all known organometallic compounds in Groups IV, V, VI, VII, and VIII.

No study has been reported concerning organomasurium compounds.

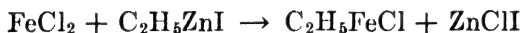
Interaction of rhenium trichloride with methylmagnesium iodide has been reported to give trimethylrhenium, an almost colorless oil, heavier than water, not very inflammable, and decomposable slowly by hydrogen peroxide to give perrhenic acid.^{128a} However, there may be as yet unexplained catalytic influences, for according to recent studies this reaction yielded almost exclusively methane and ethane.^{128b}

GROUP VIII

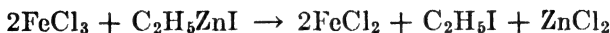
[Fe, Co, Ni, Ru, Rh, Pd, Os, Ir, Pt]

Very few organometallic compounds of Group VIII metals have been described. Apart from some organoiron compounds, for which there is indirect evidence, the only organometallic types isolated and studied in any detail have been some methylplatinum compounds.

Ethyliron chloride has been prepared from ethylzinc iodide and ferrous chloride.



The same product is obtained from ferric chloride, which presumably is first reduced to ferrous chloride.¹²⁹



Phenyliron iodide has been prepared by a corresponding reaction.¹³⁰



¹²⁸ (a) Druce, *J. Chem. Soc.*, 1129 (1934). (b) Gilman, Jones, Moore, and Kolbezen *J. Am. Chem. Soc.*, **63**, 2525 (1941).

¹²⁹ Job and Reich, *Compt. rend.*, **174**, 1358 (1922).

¹³⁰ Champetier, *Bull. soc. chim.*, **47**, 1131 (1930).

The chief evidence in support of the organoiron compounds is the formation of ferrous hydroxide on hydrolysis.

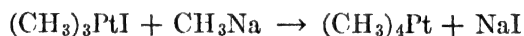


When iron halides are treated with Grignard reagents the reaction proceeds predominantly to the formation of coupling (R-R) compounds. Practically quantitative yields of biphenyl have been obtained from the reaction between phenylmagnesium iodide and halides of the Group VIII metals.^{131a} The lesser yields of biphenyl when the chlorides of osmium, iridium, and platinum are used suggest that the extent of the coupling reaction is a rough measure of the thermal instability of the immediately formed organometallic compounds, the phenylplatinum compounds being most stable.

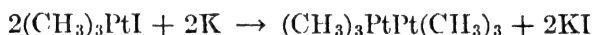
Trimethylplatinum iodide has been prepared from platinum chloride and methylmagnesium iodide.^{131b}



It was subsequently^{131c} shown that tetramethylplatinum is one of several by-products of the reaction between platinum chloride and methylmagnesium iodide. Tetramethylplatinum is prepared conveniently from trimethylplatinum iodide and methylsodium.



Hexamethyldiplatinum has been prepared by heating trimethylplatinum iodide with powdered potassium in dry benzene.^{131c}



Organopalladium compounds have been postulated as intermediates in the catalytic reduction of aryl halides.^{131d}

Hydrides, carbides, and carbonyls are known of several of the Group VIII metals.

ORGANOMETALLIC "RADICALS"

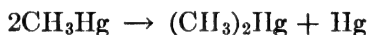
Some organometallic compounds appear to have a metal with a valence lower than normal. These so-called organometallic radicals, like triphenyllead, may possibly have a very low concentration of the radical present.



¹³¹ (a) Gilman and Lichtenwalter, *J. Am. Chem. Soc.*, **61**, 957 (1939); Kharasch and Fields, *ibid.*, **63**, 2316 (1941). (b) Pope and Peachey, *J. Chem. Soc.*, **95**, 571 (1909). (c) Gilman and Lichtenwalter, *J. Am. Chem. Soc.*, **60**, 3085 (1938). (d) Busch and Weber, *J. prakt. Chem.*, **146**, 1 (1936).

However, magnetic measurements have not revealed free radicals, and some of the earlier evidence based on molecular-weight determinations may be vitiated because of the slow decomposition of the RM compounds to fragments of relatively low molecular weight.^{132a} The special properties of such compounds may be due to a very weak metal-metal linkage. Some of the organometallic "radicals" have properties suggestive of a radical like triphenylmethyl. Such characteristics are color; marked tendency to assume a normal valence of the metal by addition of oxygen, iodine, or metals like sodium; increase in association or polymerization in more concentrated solutions; and disproportionation. Some of the "radicals" have properties, such as luster and conductance, similar to those of metals.

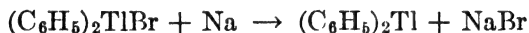
Mercury. Some alkylmercury compounds like methylmercury and ethylmercury have been prepared^{132b} by the electrolysis of alkylmercuric halides in liquid ammonia at a temperature of -60° . The radicals were deposited on the cathode, and were found to be unstable. Methylmercury, for example, shows considerable decomposition even at -33° .



This tendency of the radical to disproportionate to free metal and an organometallic compound having a metal with normal valence is shown by many organometallic radicals.

The metallic characteristics of a compound like methylmercury recall the properties of substances like tetramethylammonium, $(\text{CH}_3)_4\text{N}$. If the metallic nature of this group, which itself contains no metal, be admitted, then it becomes understandable why compounds like benzyltetramethylammonium, $\text{C}_6\text{H}_5\text{CH}_2\text{N}(\text{CH}_3)_4$, have been correlated with organometallic compounds (p. 530).

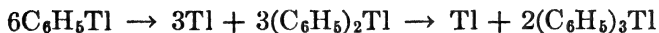
Thallium. Diphenylthallium is probably formed when one equivalent of sodium is added to a solution of diphenylthallium bromide in liquid ammonia.¹⁰⁹



There is more compelling evidence for the transitory formation of phenylthallium when triphenylthallium is heated in xylene.¹⁰⁹

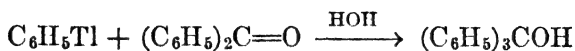


In the absence of a reactant, the phenylthallium is converted to triphenylthallium and metallic thallium, probably by way of diphenylthallium.



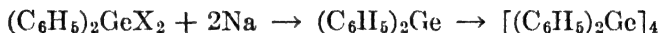
¹³² (a) Morris and Selwood, *J. Am. Chem. Soc.*, **63**, 2509 (1941). (b) Kraus, *ibid.*, **35**, 1732 (1913). (c) Kraus and Brown, *ibid.*, **52**, 4031 (1930).

Pyrolysis in xylene, in the presence of reactants like carbon dioxide, benzophenone, and benzonitrile, results in the normal additions of a moderately reactive RM compound.

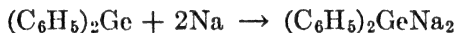


Phenylthallium, which is probably the most reactive organometallic "radical," is highly unstable thermally. When phenyllithium was added to a suspension of thallous chloride (TlCl) in ether, cooled to -70° , there was an immediate deposition of metallic thallium. The subsequent isolation of triphenylthallium indicated that phenylthallium was formed initially, but then decomposed in essential accordance with the reactions illustrated above.

Germanium. Diphenylgermanium has been prepared by the action of sodium on a diphenylgermanium dihalide in boiling xylene.^{132c}

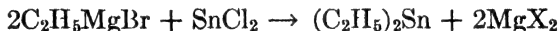
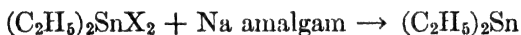


In liquid ammonia, sodium reacts with diphenylgermanium to give diphenylgermanium-disodium.

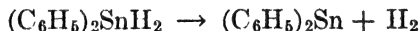


This reaction is quite general with organometallic radicals. The sodium derivatives are useful in synthesis, reacting, for example, with alkyl halides to substitute alkyl radicals for the sodium.

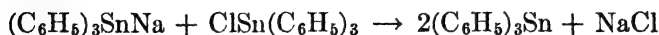
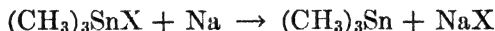
Tin. Di- and trivalent organotin compounds of both the aliphatic and the aromatic series have been prepared. Diethyltin has been synthesized in several ways, of which the following are typical.^{133a}



The diaryltin compounds have been prepared by related methods, as well as by pyrolysis of the dihydride.^{133b}



The R_3Sn compounds are conveniently prepared in liquid ammonia by reactions like the following.^{133c}



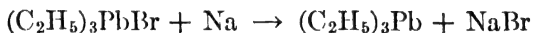
¹³³ (a) Löwig, *Ann.*, **84**, 308 (1852); Frankland, *Ann.*, **85**, 329 (1853); Pfeiffer, *Ber.*, **44**, 1269 (1911). (b) Krause and Becker, *Ber.*, **53**, 173 (1920); Chambers and Scherer, *J. Am. Chem. Soc.*, **48**, 1054 (1926). (c) Kraus and Sessions, *ibid.*, **47**, 2361 (1925); Harada, *Bull. Chem. Soc. Japan*, **4**, 266 (1929) [*C. A.*, **24**, 1340 (1930)]; Ladenburg, *Ann. (Suppl.)*, **8**, 63 (1872); Rügheimer, *Ann.*, **364**, 51 (1909); Chambers and Scherer, *J. Am. Chem. Soc.*, **48**, 1054 (1926).

In general, both the di- and trivalent organotin compounds react readily with oxygen, sulfur, and halogens to give tetravalent types.



They add sodium, as mentioned previously, and reduce salts like mercuric chloride and silver nitrate. The alkyl compounds associate or polymerize more readily than the corresponding aryl types. When the compounds are colored, the color varies with the R group: dicyclohexyltin is intensely yellow, and a benzene solution of diphenyltin becomes dark red when exposed to sunlight.

Lead. The general procedures for the preparation of so-called organolead radicals may be classified roughly as reductions and the direct introduction of R groups. The best illustrations of reduction are the preparation of triethyllead (or hexaethyldilead) by electrolysis of triethyllead hydroxide,^{134a} and the reaction of sodium in liquid ammonia with triethyllead bromide.^{134b, 135}



The direct introduction of R groups has been effected by interaction of sodium-lead alloys and alkyl halides, and by reaction of lead chloride with RMgX or RLi compounds. The usual reaction between lead chloride and RMgX compounds gives R₄Pb compounds.



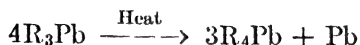
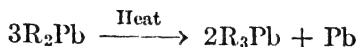
With some Grignard reagents no special procedures are necessary for the formation of the radical types. Actually, *p*-xylylmagnesium bromide gives tri-*p*-xylyllead in 50 per cent yield and no tetraaryllead. It appears likely that the di- and trivalent lead types are precursors in the formation of most R₄Pb compounds from lead chloride and the Grignard reagent or organolithium compounds.¹³⁶ This finds support in the following observations: (1) In the preparation of R₄Pb compounds the colors characteristic of R₂Pb and R₃Pb compounds are first noticed. (2) The di- and trivalent types can be isolated from such reaction mixtures. (3) The R₂Pb and R₃Pb compounds are converted to the R₄Pb compounds on the application of heat, in the presence or absence of Grignard reagent.

¹³⁴ (a) Midgley, Hochwalt, and Calingaert, *J. Am. Chem. Soc.*, **45**, 1821 (1923). See, also, Tafel, *Ber.*, **44**, 323 (1911); Renger, *Ber.*, **44**, 337 (1911); and Löwig, *Ann.*, **88**, 318 (1853). (b) Calingaert and Soroos, *J. Org. Chem.*, **2**, 535 (1938).

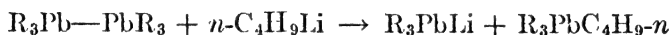
¹³⁵ Gilman and Bailie, *J. Am. Chem. Soc.*, **61**, 731 (1939).

¹³⁶ Krause and co-workers, *Ber.*, **52**, 2165 (1919); *Ber.*, **53**, 173 (1920); *Ber.*, **54**, 2060 (1921); *Ber.*, **55**, 888 (1922); Möller and Pfeiffer, *Ber.*, **49**, 2443 (1916); Goddard, *J. Chem. Soc.*, **123**, 1161 (1923); Austin, *J. Am. Chem. Soc.*, **54**, 3726 (1932).

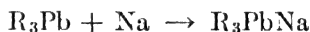
The several transformations may proceed stepwise,



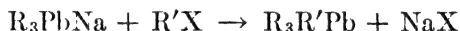
for the di- is convertible to the tri-, and the tri- to the tetravalent type. These reactions leading to the formation of an organometallic compound with the metal in a normal valence state remind one of the thermal decomposition of methylmercury to dimethylmercury and mercury. Actually, however, there may be, under certain conditions, secondary transformations in the conversion of PbCl_2 to R_4Pb . One of these with *n*-butyllithium and R_3Pb or $\text{R}_3\text{Pb}-\text{PbR}_3$ is:



The R_3Pb compounds add alkali metals in liquid ammonia.¹³⁵



The resulting dimetallic compounds are useful for the preparation of unsymmetrical $[\text{R}_3\text{R}'\text{Pb}]$ types.



Addition also takes place with the binary system, $\text{Mg} + \text{MgBr}_2 \rightleftharpoons 2\text{MgBr}$, the magnesium halide behaving in many respects like sodium.

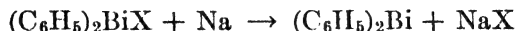


A similar reaction occurs with triphenylmethyl.¹³⁷



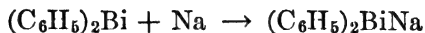
In a general way, the properties of R_2Pb and R_3Pb compounds closely resemble those of the corresponding organotin compounds. The approximate order of decreasing stability is: Aryl_3Pb , Aryl_2Pb , Alkyl_3Pb , Alkyl_2Pb . The number, kind, and position of substituents in the alkyl or aryl groups play, of course, a significant part in the properties of these several types, just as they do in organometallic compounds having a metal with normal valence.

Bismuth. When diphenylbismuth halides are treated in liquid ammonia with lithium, sodium, potassium, calcium, or barium, the following general reaction occurs.



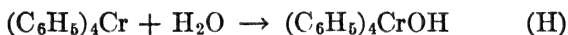
¹³⁷ Gilman and Fothergill, *J. Am. Chem. Soc.*, **51**, 3149 (1929); Gomberg and Bachmann, *ibid.*, **52**, 2455 (1930).

The intense green color of diphenylbismuth (or tetraphenyldibismuth) gives way to the characteristic deep red color of diphenylbismuth-sodium when more sodium is added.^{123c}



There is also evidence for the transient existence of dimethylbismuth and diethylbismuth.¹³⁸

Chromium. The triphenylchromium and tetraphenylchromium, mentioned with organochromium compounds, have some metallic characteristics highly remindful of compounds like methylmercury. In particular, each reacts with water with the liberation of hydrogen and the formation of the corresponding hydroxide.



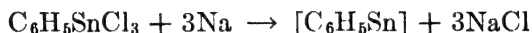
INTERCONVERSION OF ORGANOMETALLIC COMPOUNDS

There is an unusual tendency for one organometallic compound to be converted to another organometallic compound. Several of these interconversions have already been considered.

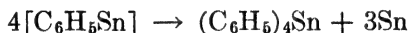
1. The so-called radicals tend to revert to organometallic compounds having the metal with a normal valence.



Phenyltin, which may be formed transitorily in the following reaction,



disproportionates¹³⁹ to tetraphenyltin and tin.



Under corresponding conditions the intermediately formed phenyl-germanium polymerizes (p. 558).

2. The equilibrium between simple and mixed compounds



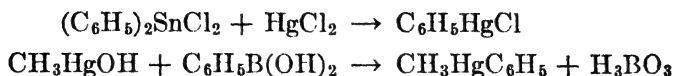
appears to be attained more rapidly with the more reactive organometallic compounds. That is, diphenylmagnesium and magnesium bromide give phenylmagnesium bromide more rapidly than tetraphenyltin and tin tetrachloride give phenyltin chlorides.

When the metal in the salt MX_2 is unlike that in the organometallic

¹²⁸ Denham, *ibid.*, **43**, 2367 (1921); Paneth and co-workers, *Ber.*, **62**, 1335 (1929); *J. Chem. Soc.*, 366 (1935).

¹³⁹ Schwarz and Reinhardt, *Ber.*, **65**, 1743 (1932).

compound, the reaction can proceed in at least two ways. Either one organometallic compound is formed exclusively,^{140a}



or a mixture of two different organometallic compounds results.^{140b}



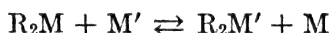
Solubility factors have pronounced effects.

3. The rate of disproportionation of unsymmetrical organometallic compounds to the symmetrical types



appears to be greater with the more reactive organometallic compounds.

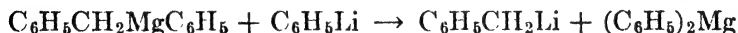
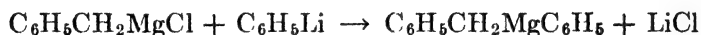
4. The following equilibrium



is generally displaced largely in that direction which gives the more reactive organometallic compound.^{141a} Numerous experiments have been carried out on the expulsion of the metal from an organometallic compound by another metal, both with and without a solvent.^{141b} The direction and extent of displacement are influenced by such factors as the ratio of reactants and the ability of the metals to form couples or amalgams. It has been suggested that some of these reactions take place by way of free radicals.^{141c}



5. The ready interchange of metals suggests the possible interconversion of two different organometallic compounds. This type of reaction has been used for the preparation of the otherwise difficultly accessible benzyl lithium.¹⁴²

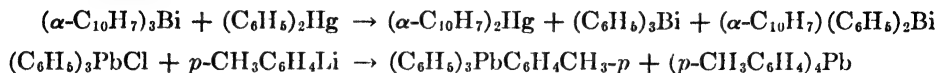


¹⁴⁰ (a) Kocheshkov and Nesmeyanov, *J. Gen. Chem. (U.S.S.R.)*, **4**, 1102 (1934) [*C. A.*, **29**, 3993 (1935)]. (b) Freidlina, Nesmeyanov, and Kocheshkov, *Ber.*, **68**, 565 (1935); Gilman and Apperson, *J. Org. Chem.*, **4**, 162 (1939).

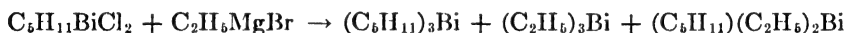
¹⁴¹ (a) Schlenk and Holtz, *Ber.*, **50**, 262 (1917); Ziegler, *Ber.*, **64**, 445 (1931). (b) Krafft and Neumann, *Ber.*, **34**, 565 (1901); Hilpert and Grüttner, *Ber.*, **45**, 2828 (1912); *Ber.*, **46**, 1675 (1913); Steinkopf and Buchheim, *Ber.*, **54**, 1030 (1921); Shurov and Rasuvaev, *Ber.*, **65**, 1507 (1932); Gilman and Marple, *Rec. trav. chim.*, **55**, 133 (1936). (c) Gilman and Brown, *ibid.*, **50**, 184 (1931); Rasuvaev and Koton, *Ber.*, **65**, 613 (1932).

¹⁴² Ziegler and Dersch, *Ber.*, **64**, 448 (1931). See, also, Schlenk and Holtz, *Ber.*, **50**, 262 (1917), and Hein and co-workers, *Z. anorg. allgem. Chem.*, **141**, 161 (1924).

The benzylphenylmagnesium, which is probably formed as an intermediate, might be expected to disproportionate to dibenzylmagnesium and diphenylmagnesium, in which event, the precursory active agent would be dibenzylmagnesium. Some other illustrative interconversions of two different organometallic compounds follow: ^{143a}

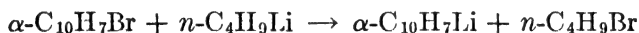


This last reaction illustrates an interchange of radicals resulting in the formation of but one class of organometallic compounds, the organo-lead compounds. A related reaction ^{143b} is:



A more complete account of recent studies in the interconversion or redistribution reaction of some types mentioned in this section is given in Chapter 24.

6. The replacement of radicals has also been observed where but one organometallic compound is involved.



This type of halogen-metal interconversion reaction is discussed on p. 538.

7. There are special reactions for the conversion of one type of organometallic compound to another type,



as well as the many general reactions previously considered such as the conversion of an R_4M type to R_3MX , R_2MX_2 , and RMX_3 compounds by the action of halogens and halogen acids. A special reaction involving carbides is the formation of some methylmetallic compounds from aluminum carbide and salts of heavy metals like mercuric chloride, stannic chloride, and bismuth chloride. ¹⁴⁴



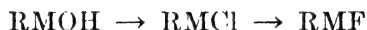
The relatively ready interconversion of organometallic compounds suggests ionic reactions. However, only the more reactive organo-

¹⁴³ (a) Frankland, *Ann.*, **111**, 44 (1859); Challenger and Ridgway, *J. Chem. Soc.*, **121**, 104 (1922); Austin, *J. Am. Chem. Soc.*, **54**, 3726 (1932). (b) Norvick, *Nature*, **135**, 1038 (1935). See, also, Challenger, *J. Chem. Soc.*, **105**, 2210 (1914), and Kocheshkov, Nesmeyanov, and Pusyrewa, *Ber.*, **69**, 1639 (1936).

¹⁴⁴ Hilpert and Ditmar, *Ber.*, **46**, 3738 (1913)

metallic compounds are appreciably dissociated (p. 530). Some studies have been carried out to determine whether there is slight ionization with the relatively unreactive organometallic compounds (Chapter 24). When radioactive lead salts, like lead chloride and lead acetate, are heated with non-radioactive organolead compounds, like tetraphenyllead, there is no exchange of lead atoms. When dissociable inorganic salts with different acid radicals are used, there is an exchange between the active and inactive salts.^{145a} More recent studies have indicated a transference of atoms with organometallic compounds. By means of the radioactive indicator method, using radioactive isotopes to show an exchange of atoms, evidence has been obtained which suggests that both radioactive lead and radioactive bismuth can exchange with lead in tetramethyllead and bismuth in trimethylbismuth, respectively, in ether solution at room temperature. Because the exchange is not shown with trimethylamine, tetramethylsilicon, and tetramethyltin it is probable that the transference occurs mainly with atoms of the same atomic number, and without a break-up of the molecule which would be expected if free radicals were involved.^{145b}

Although the evidence for ionic reactions in interconversions is weak, particularly where different organometallic compounds are involved, it is more likely that ionic reactions are involved in the exchange of acid radicals in mixed organometallic compounds. In a compound like RMX there may be interconversions (a) of the R group, (b) of the metal, and (c) of the X group. Actually, all three kinds are known, and the first two have been mentioned. The following illustrative transformations of X groups are readily effected.



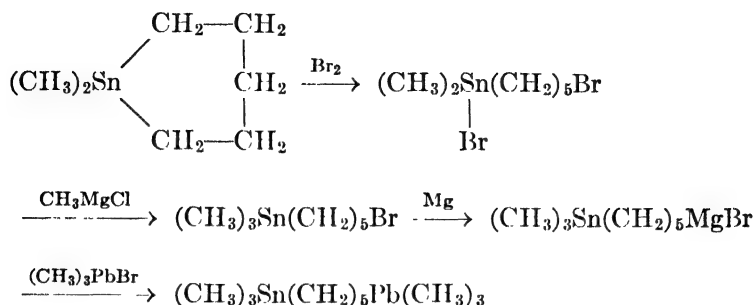
Incidentally, the relative stabilities of compounds like $(\text{C}_6\text{H}_5)_3\text{BiX}_2$, where X is halogen or a pseudo-halogen, are almost exactly in the order determined by the decomposition potentials of the potassium salts in water:¹⁴⁶ F, ONC, OCN, Cl, N_3 , Br, CN, SCN, I, SeCN, TeCN. The fluoride is most stable, and a compound like $(\text{C}_6\text{H}_5)_3\text{BiI}_2$ is extremely unstable. The $(\text{C}_6\text{H}_5)_2\text{BiX}$ compounds have apparently an order of stability which is the inverse of the order of stability of $(\text{C}_6\text{H}_5)_3\text{BiX}_2$ compounds.

Finally, mention should be made of the formation of an organometallic compound having two or more different metals from an organo-

¹⁴⁵ (a) Hevesy and Zechmeister, *Ber.*, **53**, 410 (1920). (b) Leigh-Smith and Richardson *Nature*, **135**, 828 (1935).

¹⁴⁶ Challenger and Richards, *J. Chem. Soc.*, 405 (1934).

metallic compound with but one metal. The following reactions illustrate the first synthesis of this kind:¹⁴⁷



PHYSIOLOGICAL PROPERTIES

As a broad generalization it may be stated that organometallic compounds are relatively highly toxic. Little is known of the odor and taste of the moderately and highly reactive organometallic compounds, partly because of their slight volatility and more particularly because the aqueous medium presumably necessary for these sense perceptions is ideally suited for decomposing the reactive organometallic compounds. Because of the known toxicity of the slightly reactive and more volatile organometallic compounds, no intentional taste test comparisons have been reported. The odors of such compounds are better known, and they vary over wide limits. Some have a pleasant fruity bouquet and others are highly obnoxious; some are without any appreciable odor and others have ill-defined "characteristic odors." There are highly purified RM compounds which develop an odor only after brief contact with the atmosphere. Some chemists who have worked closely with particular types can detect minimal quantities by a characteristic odor, as, for example, the lower-molecular-weight dialkylmercury compounds.

Although it is true that organometallic compounds are generally quite toxic, it is equally true that there are marked variations in toxicity. The variations are noted with different classes of organometallic compounds and also within the same class, depending on the alterations in structure of the R groups and the nature of X or the acid radical. This makes it understandable why some organometallic compounds have actually found application as therapeutic agents and why others are being investigated for their possible curative effects. Organoantimony and organobismuth compounds have been used in trypanosome

¹⁴⁷ Grüttner and Krause, *Ber.*, **50**, 1549 (1917).

infections;^{148a} organomercury compounds as disinfectants and diuretics;^{148b} organolead compounds in the treatment of cancer;^{148c} and organogold compounds in the treatment of tuberculosis and arthritis. Organometallic compounds have also been used in veterinary medicine in the treatment of some forms of coccidiosis, and in botany as seed disinfectants to prevent smut diseases of cereals.

If correlations may be drawn between metallic hydrides and organometallic compounds, one may conclude that the physiological effects of organometallic compounds are not necessarily related to the physiological effects of the metal alone or to inorganic salts of the metals. For example, tin hydride is the most toxic of all hydrides so far investigated, whereas metallic tin and tin salts are apparently without any significant harmful effect on the organism.^{148d} However, lead and its many compounds are generally toxic.

General biological applications of organometallic compounds have been surveyed recently.¹⁴⁹ Indirect but significant contributions of organometallic compounds in biological problems have been their application in studies of reaction mechanisms and in procedures concerned with the structure and preparation of compounds like vitamins, hormones, carcinogens, and other biologically potent materials.

APPLICATIONS

Undoubtedly the greatest value of organometallic compounds is their laboratory use for synthesis. The most important technical application is that of tetraethyllead as an anti-knock compound.* It is doubtful that any other group of organic compounds combines at the same time an astonishingly high utility in the laboratory with an equally low usefulness in the works. With increasing reductions in the cost of metals and their salts and with newer solvents or with techniques to reduce the need of solvents, it is rather likely that industrial uses for organometallic compounds will expand.

Organometallic compounds provide an excellent bridge between inorganic and organic chemistry. The contributions of organometallic

¹⁴⁸ (a) Levaditi and Lépine, *Compt. rend.*, **193**, 404 (1931). (b) Slotta and Jacobi, *J. prakt. Chem.*, **120**, 249 (1929). (c) Bischoff and co-workers, *J. Pharmacol.*, **34**, 85 (1928); Krause, *Ber.*, **62**, 135 (1929). (d) Paneth and Joachimoglu, *Ber.*, **57**, 1925 (1924); Stock and Guttman, *Ber.*, **37**, 885 (1904).

¹⁴⁹ Gilman, *Science*, **93**, 47 (1941). Among the good books containing accounts of the physiological action of metals and their compounds are: Heffter and Heubner, "Handbuch der experimentellen Pharmakologie," Berlin (1935); and Fischl and Schlossberger, "Handbuch der Chemotherapie," Leipzig (1934).

* Tetraethyllead also has a catalytic effect on various reactions: Gilman and St. John, *Rec. trav. chim.*, **49**, 222 (1930); Vaughan and Rust, *J. Org. Chem.*, **5**, 449 (1940).

compounds to inorganic chemistry have been significant, but less numerous than to organic chemistry. There are occasional syntheses and analyses of inorganic compounds by means of organometallic compounds, but the outstanding uses have been on problems concerned with valence, atomic structure, chain reactions *via* free radicals, and correlations of physical properties.¹⁵⁰

In addition to the synthetic applications in organic chemistry, organometallic compounds have found extensive application in analysis (the Tschugaeff-Zerewitinoff procedure) and in the characterization by derivatives of some classes of organic compounds. Organometallic compounds have been used to broaden our knowledge of many reaction mechanisms such as 1,4-addition, allylic rearrangements, rubber vulcanization,¹⁵¹ and reduction by sodium and alcohol, as well as many of the condensations effected by sodium.¹⁵² Several series of radicals and compounds have been developed by means of organometallic compounds: the series of radicals based on hydrogen chloride cleavage; the series of functional groups arranged according to relative reactivities; and the series of extremely weak acids.

Biologically, the organometallic compounds have found use as pharmaceutical agents and insecticides.¹⁴⁹ Perhaps the most suggestive idea from a biological viewpoint is that by Willstätter^{153a} on chlorophyll: the magnesium linkage in chlorophyll may resemble that present in Grignard reagents and be a significant point of reaction with carbon dioxide in photosynthesis.^{153b} One may then speculate that some of the subsequently necessary reductions and condensations leading to carbohydrates may also involve Grignard-like transformations. To continue speculatively, the biologically important catalyst for synthesis, hemoglobin, may function as an oxygen carrier, possibly by means of peroxide formation due to an organoiron complex.^{153c}

From the viewpoint of organic chemistry it is quite likely that some

¹⁵⁰ (a) v. Grosse, *Z. anorg. allgem. Chem.*, **152**, 133 (1926). (b) Jones, Evans, Gulwell, and Griffiths, *J. Chem. Soc.*, 39 (1935); Terenin, *J. Chem. Phys.*, **2**, 441 (1934); Thompson, *J. Chem. Soc.*, 790 (1934); Thompson and Frewing, *Nature*, **135**, 507 (1935); Garzuly-Janke, *J. prakt. Chem.*, **142**, 141 (1935); Pai, *Proc. Roy. Soc. (London)*, **A149**, 29 (1935) [*C. A.*, **29**, 3913 (1935)]; Thompson and Linnett, *Trans. Faraday Soc.*, **32**, 681 (1936) [*C. A.*, **30**, 4371 (1936)]; Brockway and Jenkins, *J. Am. Chem. Soc.*, **58**, 2036 (1936); Smyth, *J. Org. Chem.*, **6**, 421 (1941). See, also, Dermer, *Chem. Rev.*, **14**, 385 (1934), for an excellent correlation of organometallic compounds with metallic salts of alcohols and alcohol analogs.

¹⁵¹ Midgley, Henne, and Shepard, *J. Am. Chem. Soc.*, **56**, 1156 (1934).

¹⁵² Chelintzev and Osetrova, *Ber.*, **69**, 374 (1936).

¹⁵³ (a) Willstätter, *Ann.*, **350**, 64 (1906). (b) It is interesting to note that recent studies [Ruben and Kamen, *J. Am. Chem. Soc.*, **62**, 3451 (1940)] report the isolation of high-molecular-weight acids from photosynthetic reactions. (c) See Kunz and Kress, *Ber.*, **60**, 367 (1927), for an indigo-iron complex which takes up and gives off oxygen.

of the significant contributions of organometallic compounds in the near future will continue along synthetic lines but on a broader basis of more highly selective preferential reactions with compounds having polyfunctional groups. The gradations in properties of organometallic compounds appear to be such as to warrant the expectation of more selective reactions. Obviously, newer types of organometallic compounds should help bridge some of the present gaps in effecting preferential reactions. One may predict that organometallic compounds of all the metals will be prepared. The development of organometallic chemistry has provided numerous hypotheses concerning the limits of preparation of these compounds. Gradually, the hypotheses have been narrowed down so that fewer and fewer metals are included in the groups which are said to be incapable of forming organometallic compounds. Some of these earlier hypotheses have been useful in pointing out those organometallic compounds which will be prepared with difficulty; other hypotheses have undergone revision necessitated by the preparation of organometallic compounds the existence of which had been denied.^{150a}

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CHAPTER 6

FREE RADICALS

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INTRODUCTION

History of Free Radicals. During the early decades of the nineteenth century the idea of radicals, introduced by Lavoisier in 1785, played an important part in the development both of the theoretical and experimental side of organic chemistry. Several prominent investigators, among them Liebig, expressed the conviction that radicals like methyl and ethyl could be and would be isolated in a free state. Experimental evidence in favor of this view was not lacking. In 1815 Gay-Lussac¹ prepared cyanogen gas, and, when analysis showed the gas to have the composition CN, it was believed that the free cyanogen radical itself had been obtained. In 1841 Bunsen² reported the isolation of the free cacodyl radical $(\text{CH}_3)_2\text{As}$ from the reaction between cacodyl chloride $(\text{CH}_3)_2\text{AsCl}$ and zinc. Frankland³ (1848-1850) produced what he believed to be free ethyl by abstracting the halogen atom from ethyl iodide by means of zinc, and in like manner he prepared "methyl" and "amyl." Similar "radicals" were obtained by Kolbe⁴ by electrolysis of the salts of fatty acids. In 1850 Frankland announced that the isolation of these "radicals" disposed of all doubt as to their actual existence.

It was not until 1864, after Cannizzaro had made clear the distinction between atoms and molecules, that it was shown that the so-called radicals, cyanogen, cacodyl, methyl, and the like, had molecular weights double that of the radical and were compounds of the type $\text{NC}-\text{CN}$, $(\text{CH}_3)_2\text{As}-\text{As}(\text{CH}_3)_2$, and CH_3-CH_3 . With the advent of the structural theory based on the unvarying quadrivalence of carbon, it was considered that radicals were incapable of existence, and this view was held for the next forty years (1860-1900). It is true that Nef⁵ in the last decade of the nineteenth century sought to prove that free radicals, especially those containing bivalent carbon, were intermediates in chemical reactions, but the general opinion was given expression in Ostwald's comment in 1896, "It took a long time before it was finally recognized that the very nature of the organic radicals is inherently such as to preclude the possibility of isolating them."

Four years later (1900) M. Gomberg at the University of Michigan announced the discovery of the free radical triphenylmethyl $(\text{C}_6\text{H}_5)_3\text{C}$.

¹ Gay-Lussac, *Ann. chim.*, **95**, 156 (1815).

² Bunsen, *Ann.*, **37**, 31 (1841).

³ Frankland, *Ann.*, **71**, 171 (1849); **74**, 41 (1850); **77**, 221 (1851).

⁴ Kolbe, *Ann.*, **69**, 257, 279 (1849).

⁵ Nef, *Ann.*, **270**, 268 (1892); **287**, 265 (1895); **298**, 202 (1897).

The goal of the earlier chemists had been attained. More important, however, than simply marking the end of the quest for free radicals, the discovery of triphenylmethyl initiated the study of a most important type of compound of significance in all branches of chemistry.

Discovery of Triphenylmethyl. In 1897 Gomberg⁶ had succeeded in synthesizing tetraphenylmethane $(C_6H_5)_4C$ for the first time. This hydrocarbon yielded a tetranitro derivative which, unlike the nitro derivative of triphenylmethane, gave no color with an alcoholic solution of potassium hydroxide. In order to determine whether this test was reliable for detecting the presence or absence of a hydrogen atom on the methane carbon, Gomberg⁷ decided to prepare the completely phenylated ethane, hexaphenylethane $(C_6H_5)_3C-C(C_6H_5)_3$, and learn the behavior of its hexanitro derivative with alcoholic potassium hydroxide. It seemed that this hydrocarbon could be made easily by interaction of triphenylchloromethane and a metal.

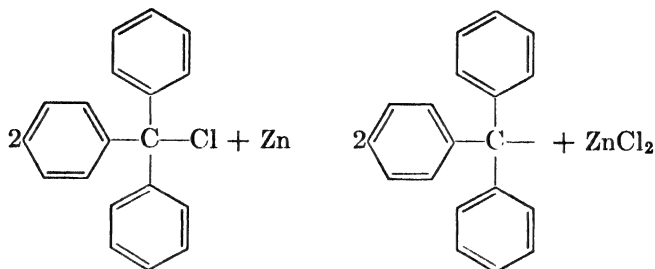


By heating a benzene solution of triphenylchloromethane with silver he obtained a colorless solid whose high melting point and sparing solubility were analogous to the properties of tetraphenylmethane. Repeated analysis, however, indicated that the compound contained oxygen. That this conclusion was correct and, furthermore, that the oxygen came from the air were shown by running the reaction in an atmosphere of carbon dioxide. Under these conditions the oxygen compound did not form and evaporation of the solution yielded a crystalline hydrocarbon whose composition corresponded to that of hexaphenylethane. The same hydrocarbon was isolated when the silver was replaced by mercury or zinc.

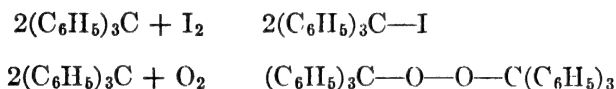
The properties of the hydrocarbon were entirely different from those of a substituted ethane. Gomberg reported: "The compound is extremely unsaturated. A solution of it in benzene or in carbon disulfide absorbs oxygen with great avidity and gives an insoluble oxygen compound. It absorbs chlorine, bromine and iodine. . . . The experimental evidence . . . forces me to the conclusion that we have to deal here with a free radical triphenylmethyl $(C_6H_5)_3C\cdot$. On this assumption alone do the results become intelligible and receive an adequate explanation. The action of zinc results, as it seems to me, in a mere abstraction of the halogen.

⁶ Gomberg, *Ber.*, **30**, 2043 (1897); *J. Am. Chem. Soc.*, **20**, 773 (1898).

⁷ Gomberg, *ibid.*, **22**, 757 (1900); *Ber.*, **33**, 3150 (1900).



Now, as a result of the removal of the halogen atom from triphenylchloromethane, the fourth valence of the methane is bound either to take up the complicated group $(\text{C}_6\text{H}_5)_3\text{C}-$ or remain as such, with carbon as trivalent. Apparently, the latter is what happens." On this basis the extreme reactivity of the hydrocarbon was easily explained: the trivalent carbon tends to become quadrivalent and does so by combining with other compounds.



Chemical reactions alone could not exclude the hexaphenylethane structure, and so determinations of the molecular weight were employed to decide whether the hydrocarbon was a free radical or its bimolecular form. The results indicated that the colorless solid hydrocarbon was hexaphenylethane, which in solution dissociates into triphenylmethyl radicals until an equilibrium is established.



The identical equilibrium mixture was obtained from both directions: by association of the free radicals as they were formed from triphenylchloromethane, and by dissociation of the previously isolated hexaphenylethane.

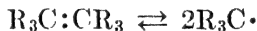
The important observation was made that the free radicals are colored while the hexaphenylethane is colorless, and this property of color proved useful in observing the progress of dissociation and in detecting the presence of the free radicals. When the colorless hexaphenylethane is dissolved, the solution remains colorless for a few seconds and then begins to turn yellow. In a short time the color reaches a permanent intensity as the equilibrium point is reached. With certain concentrations, it is possible to remove the yellow color by reaction of the free radicals with oxygen and then observe the regeneration of the color as more free radicals are formed by dissociation.

A large number of hexaarylethanes were prepared which contained a variety of aryl groups, and it was found that all of them possessed the property of dissociating into colored free radicals. With the establishment of the actual existence of free radicals which contain carbon linked to only three groups, investigations were launched to determine whether other elements could function in a similar manner. These ventures were successful, and free radicals are now known in which nitrogen, oxygen, and sulfur are linked to an abnormal number of groups.

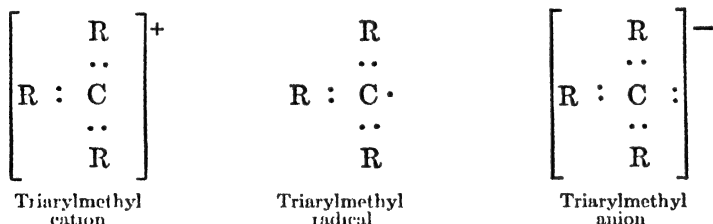
FREE RADICALS WHICH CONTAIN CARBON LINKED TO THREE GROUPS

Triarylmethyls

Nature of the Free Radicals. Free radicals such as the triarylmethyls are neutral molecules, which, unlike ions, do not possess a charge. The dissociation of a hexaarylethane is a non-ionic process in which the shared pair of electrons between the ethane carbon atoms becomes divided equally between the two radicals, a process similar to the formation of two neutral atoms from a diatomic molecule. As a result a triarylmethyl radical contains an unpaired electron.



The ions of the triarylmethyl group result by ionization of certain salts as R_3CX (R = aryl; X = sulfate, nitrate, etc.) which give the cation $(\text{R}_3\text{C})^+$, and R_3CNa which yield the anion $(\text{R}_3\text{C})^-$. Electronically (p. 1928) the three species—cation, free radical, and anion—may be represented as follows:

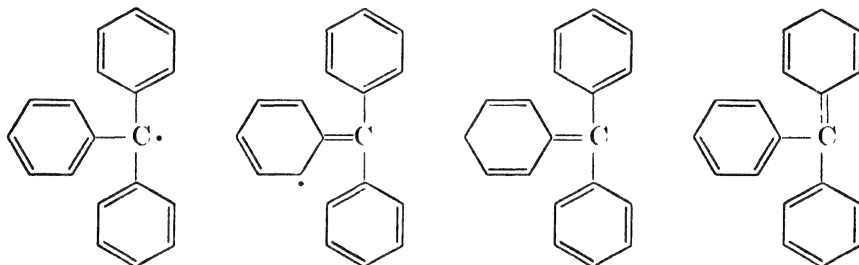


The ions do not exhibit the unsaturated behavior of the neutral free radicals. Frequently the color of the ions differs from that of the corresponding free radical; thus, the triphenylmethyl anion is intensely red while the triphenylmethyl radical is yellow.

It is almost universally true that molecules contain an even number of electrons and as a result are diamagnetic. Among the inorganic compounds only a few (among them NO , NO_2 , and ClO_2) contain an odd

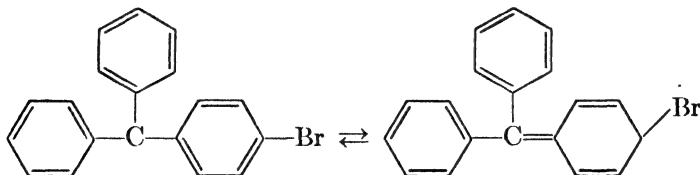
number of electrons. Such compounds (called "odd molecules" by G. N. Lewis⁸) are paramagnetic (i.e., they are attracted by a magnet) in virtue of the magnetically non-compensated electron. Indeed, free radicals have been defined as compounds which contain magnetically non-compensated electrons.⁹ This property of paramagnetism has proved useful in detecting free radicals, and it serves as a basis of one of the methods employed to determine the degree of dissociation of hexaarylethanes (p. 587).

According to the modern theory of resonance (p. 1979) the odd electron does not remain on the central carbon atom but can resonate among nine other positions (the six *ortho* and three *para* positions of the three phenyl groups). These ten structures contribute to the resultant resonance state. Several such structures are shown in the following formulas:



This resonance leads to an increased stability of the free radical.

Mention has been made of the color of the triarylmethyls. Gomberg attributed the color to the presence of a quinoid form of the free radical which is in equilibrium with the benzenoid form. Evidence in favor of quinoidation was adduced from a study of the action of silver on diphenyl-*p*-bromophenylmethyl and related compounds.¹⁰ The colorless compound diphenyl-*p*-bromophenylmethane (or the carbinol or alkyl ether) which is not subject to quinoidation loses no trace of its bromine when shaken with metallic silver. From the corresponding radical, however, the bromine is readily removed, and this is explained on the basis of the equilibrium between the two forms.



⁸ Lewis, "Valence and the Structure of Atoms and Molecules," Chemical Catalog Co. New York (1923); *Chem. Rev.*, **1**, 231 (1934).

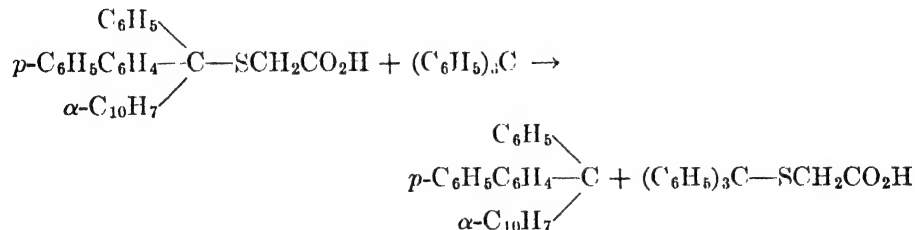
⁹ Kuhn, *Naturwissenschaften*, **22**, 808 (1934).

¹⁰ Gomberg, *Ber.*, **40**, 1847 (1907); Gomberg and Blicke, *J. Am. Chem. Soc.*, **45**, 1765 (1923).

In the quinoid form the bromine atom, no longer held by an aromatic carbon, is sufficiently reactive to combine with the metal. The fact that the same light absorption is shown by an ether solution of triphenylmethyl and ether solutions of benzoquinone, quinonemonoxime, and the like¹¹ is considered to be confirmation of the quinoid structure.

According to the resonance theory the quinoid form of Gomberg is only one of the nine similar structures contributing to the final resonance state. G. N. Lewis has pointed out that the absorption of light in the visible region is a property common to all odd molecules except nitric oxide.⁸ Recently, with Calvin,¹² he has suggested an explanation for the color of the triarylmethyls in terms of the effect produced by the presence of the unpaired electron. It must be admitted that a complete and entirely satisfactory explanation for the color is still lacking.

A number of investigators have attempted to prepare free radicals from optically active starting materials in order to determine whether the optical activity would be retained by the radical (p. 383). Persistence of the optical activity would mean that the unshared electron can preserve the tetrahedral configuration of the molecule. In one experiment triphenylmethyl was used to liberate phenyl-*p*-biphenyl- α -naphthylmethyl from optically active *l*-phenyl-*p*-biphenyl- α -naphthylthioglycolic acid.



It was found that the optical activity of the solution disappeared as the phenyl-*p*-biphenyl- α -naphthylmethyl radical was formed. From this and other results it was concluded that free radicals cannot maintain the asymmetric configuration.¹³ It should be noted that quinoidation or resonance precludes the existence of optically active triarylmethyls since the central carbon atom becomes linked by a double bond to one of the rings.

Degree of Dissociation of Hexaarylethanes. Three methods have been employed to determine the extent to which hexaarylethanes dissociate into free radicals in solution. In the earlier work, the molecular-weight method was used. In recent years methods based on the absorption of light in the visible region and on the paramagnetism of the free

¹¹ Anderson, *J. Am. Chem. Soc.*, **57**, 1673 (1935).

¹² Lewis and Calvin, *Chem. Rev.*, **25**, 273 (1939).

¹³ Wallis and Adams, *J. Am. Chem. Soc.*, **55**, 3838 (1933).

radicals have been employed. In harmony with other binary dissociation processes, the degree of dissociation of a given hexaarylethane depends on the three factors, temperature, concentration, and solvent. A check on the reliability of the methods can be applied in the form of the dissociation constants, which should remain constant over a wide range of concentration in a given solvent at the same temperature. For the binary dissociation process, $R_3C-CR_3 \rightleftharpoons 2R_3C$; $K = 4\alpha^2/(1 - \alpha)v$, where K is the dissociation constant, α the fraction of the hexaarylethane dissociated, and v the volume in liters containing a mole of the hexaarylethane.

If the molecular weight of a hexaarylethane in solution is determined by the cryoscopic or ebullioscopic method, a value is obtained which lies between that calculated for the hexaarylethane (M_c) and that for the triarylmethyl. From this value for the apparent molecular weight (M_a), the fraction (α) of hexaarylethane dissociated may be calculated from the formula: $\alpha = (M_c/M_a) - 1$; the percentage of dissociation is equal to 100α . From a critical analysis of the data reported by this method Walden¹⁴ concluded that within certain limits satisfactory values for the dissociation constant can be obtained in a given solvent. In some instances, however, there is a "drift" in the values. The molecular-weight method is limited in that values in a given solvent can be obtained only at two temperatures, the freezing point and boiling point of the solvent.

In the second method use is made of the fact that the solutions of the hexaarylethanes do not obey Beer's law. According to this law, the absorption of light should remain constant on dilution provided that no change in structure or dissociation takes place, for the number of absorbing molecules remains the same. Thus, if a colored solution contained in an upright cylinder is viewed from above, the intensity of the color will remain the same when solvent is added to the solution, because the dilution is exactly compensated by the greater thickness of the layer through which the light passes. If on dilution the intensity of the color increases, it means that the number of absorbing molecules has increased. Piccard¹⁵ demonstrated that the color of a solution containing a mixture of a hexaarylethane and the triarylmethyl radicals increased in intensity as the solution was diluted. That the increased color was the result of a simple binary dissociation process followed from the fact that the relationship between the change in intensity of the color and the variation in concentration conformed to the Ostwald dilution law, at least in dilute solutions.¹⁶

¹⁴ Walden, "Chemie der freien Radikale," Hirzel, Leipzig (1924).

¹⁵ Piccard, *Ann.*, **381**, 347 (1911).

¹⁶ Wooster, *J. Am. Chem. Soc.*, **58**, 2156 (1936).

Ziegler and Ewald¹⁷ have made use of this relationship to determine the degree of dissociation of hexaphenylethane under various conditions. By measuring the molecular extinction coefficients E_v of the colored solutions at various dilutions by means of a spectrophotometer, they determined the degree of dissociation, using the expression $\alpha = E_v/E_\infty$, where E_∞ is the molecular extinction coefficient at infinite dilution, obtained by extrapolation. By this method they obtained the results shown in Table I for hexaphenylethane in benzene at 20°. The value of K , about

TABLE I
DISSOCIATION OF HEXAPHENYLETHANE
 v = volume in liters containing 1 mole of hexaphenylethane

| | | | | | | |
|-----------------------------------|------|-----|------|--------|--------|----------|
| v | 12.5 | 98 | 885 | 25,700 | 76,000 | ∞ |
| % Dissociation (100α)... | 3.6 | 9.6 | 25.8 | 77.5 | 90 | 100 |

4.1×10^{-4} , remained constant when the solution was diluted from 1 to 6100.

An increase in temperature causes an increase in the dissociation of hexaphenylethane. Thus, a 0.07 per cent benzene solution of hexaphenylethane contains 18 per cent of triphenylmethyl at 13° ($K = 2.6 \times 10^{-4}$), about 30 per cent at 30° ($K = 7.84 \times 10^{-4}$), and 42 per cent at 43° ($K = 18.8 \times 10^{-4}$). Similar results were observed in a number of different solvents.

The effect of the solvent on the dissociation may be shown by a comparison of the dissociation constants for hexaphenylethane in a number of solvents. The solvents and the values obtained for $K \times 10^4$ at 20° were: propionitrile, 1.2; ethyl benzoate, 1.7; acetone, 1.7; dioxane, 2.5; bromobenzene, 3.7; ethylene dibromide, 3.9; benzene, 4.1; chloroform, 6.9; and carbon disulfide, 19.2.

The third method of determining the extent of dissociation, first suggested by Taylor,¹⁸ consists in measuring the paramagnetic susceptibility of a solution containing the free radical. It has been calculated that the paramagnetic susceptibility arising from the spin of one unpaired electron should be equal to 1260×10^{-6} unit per mole of free radical at 20°. From the observed magnetic susceptibility of a solution it is possible to calculate the concentration of the free radical and hence the degree of dissociation of the hexaphenylethane.¹⁹

¹⁷ Ziegler and Ewald, *Ann.*, **473**, 163 (1929).

¹⁸ Taylor, *J. Am. Chem. Soc.*, **48**, 858 (1926).

¹⁹ Roy and Marvel [*ibid.*, **59**, 2622 (1937)] have described an apparatus and procedure for measuring the paramagnetic susceptibilities of solutions of free radicals by the Quincke hydrostatic method.

One of the most influential factors affecting the dissociation of hexaarylethanes is the nature of the aryl groups attached to the central carbon atoms. This is readily apparent from a comparison of the degree of dissociation of various hexaarylethanes under similar conditions. In Table II are given the values which have been obtained by the cryoscopic method in benzene (5°C.) at approximately the same concentration (about 0.08 molar, which corresponds to about 1-3 per cent solutions of the hexaarylethanes).

TABLE II
DISSOCIATION OF HEXAARYLETHANES

| Radicals Formed | Color of Radicals | Dissociation of Ethane, % ^a |
|---|-------------------|--|
| Triphenylmethyl..... | Orange-yellow | 1-3 |
| 9-Phenylfluoryl..... | Brown (100°) | 0 |
| Diphenyl- <i>p</i> -anisylmethyl..... | Deep red | 20-25 |
| Diphenyl- <i>o</i> -anisylmethyl..... | Reddish brown | 25-30 |
| Diphenyl- β -naphthylmethyl..... | Wine-red | 7-9 ^b |
| Diphenyl- α -naphthylmethyl..... | Deep red-brown | 28-31 ^b |
| Diphenyl-1-phenanthrylmethyl..... | Deep red | 32-36 ^b |
| Tri- <i>o</i> -anisylmethyl..... | Orange | 95-100 |
| Phenyl- <i>p</i> -biphenyl- α -naphthylmethyl..... | Deep red-brown | 90-100, 54 ^c |
| Diphenyl- <i>p</i> -biphenylmethyl..... | Orange-red | 13-16 ^b |
| Phenyldi- <i>p</i> -biphenylmethyl..... | Red | 18 ^c |
| Tri- <i>p</i> -biphenylmethyl..... | Deep violet | 100, 74 ^b , 54 ^c |

^a Except as indicated, values are from Walden, "Chemie der freien Radikale," Hirzel, Leipzig (1924).

^b Recent values obtained by Bachmann and Klotzel [*J. Org. Chem.*, **2**, 356 (1938)]; the values for diphenyl- β -naphthylmethyl and diphenyl- α -naphthylmethyl are lower than those reported previously (30-35 and 55-60 per cent, respectively). The lower values have been checked by Marvel and co-workers (unpublished results) by magnetic susceptibility measurements.

^c From magnetic susceptibility measurements at 30° by Marvel and co-workers (unpublished results). The value for tri-*p*-biphenylmethyl was obtained in a 0.0125 *M* solution.

From the values in the table it is apparent that all the aryl groups, with the exception of the 9-fluoryl group, are more effective than phenyl groups in promoting dissociation. Di-(9-phenylfluoryl) is a relatively stable hydrocarbon; its solution is colorless at room temperature and contains appreciable amounts of free radicals only at higher temperatures. The 1-phenanthryl, α -naphthyl, and *o*- and *p*-anisyl groups are particularly effective in promoting dissociation. A few hexaarylethanes dissociate completely in 1-3 per cent solutions; included in this group is hexa-*p*-biphenylethane.²⁰ Paramagnetic measurements have indicated

²⁰ Schlenk, Weickel, and Herzenstein, *Ann.*, **372**, 1 (1909). But see Bachmann and Klotzel (note *b* of Table II) and Marvel who were unable to check this result.

that even the violet-colored solid hydrocarbon is the free tri-*p*-biphenylmethyl radical.²¹ Similarly, it has been reported that tri-*p*-nitrophenyl-*n*-ethyl is a unimolecular free radical in the solid state.

Paramagnetic measurements on a series of hexa-*p*-alkylphenylethanes (the same alkyl group was present on each phenyl group) in which the alkyl groups were methyl, ethyl, *n*-propyl, isopropyl, *sec*.-butyl, and isobutyl indicated that these compounds dissociated to the extent of about 15–30 per cent in 0.1 molar solutions in benzene at 30°.²² Under practically the same conditions, the free radicals diphenyl-*p*-cyclohexylphenylmethyl and phenyldi-*p*-cyclohexylphenylmethyl were formed to the extent of about 10 per cent from the corresponding hexaarylethanes; at the same temperature but in a 0.01 molar solution of the hexaaryl-ethane, tri-*p*-cyclohexylphenylmethyl was formed to the extent of 50 per cent. From these results it is evident that alkyl groups in the *para* position have a marked effect in increasing the dissociation of hexa-phenylethane.

An interesting comparison of the effect of alkyl groups was obtained by determining the degree of dissociation of a series of *sym*.-di-(alkylphenyl)-tetraphenylethanes (about 0.1 molar benzene solutions at 30°) which differed in the nature and position of the alkyl group. The larger

TABLE III
sym.-DI-(ALKYLPHENYL)-TETRAPHENYLETHANES

| Alkyl Group | Dissociation, % |
|--------------------------------|-----------------|
| <i>p</i> -Methyl | 5 |
| <i>o</i> -Methyl | 25 |
| <i>p</i> -isopropyl | 8–10 |
| <i>p</i> - <i>tert</i> .-butyl | 8–9 |

groups are somewhat more effective than the methyl group in promoting dissociation, and the methyl group is much more effective in the *ortho* than in the *para* position; in the *meta* position the methyl group has an intermediate effect.

The individual groups can be arranged roughly in the following order of influence on dissociation: 1-phenanthryl, α -naphthyl, *o*-anisyl > *p*-anisyl > $\frac{1}{2}$ xanthyl > *p*-biphenyl > β -naphthyl > *p*-alkylphenyl > phenyl > *p*-chlorophenyl > $\frac{1}{2}$ 9-fluoryl.

²¹ Müller, Müller-Rodloff, and Bunge, *Ann.*, **520**, 235 (1935).

²² Marvel, Mueller, Himel, and Kaplan, *J. Am. Chem. Soc.*, **61**, 2771 (1939).

Energies of Dissociation and Activation. The heat of dissociation of a hexaarylethane can be calculated from the change in the dissociation constant of the system $R_3C-CR_3 \rightleftharpoons 2R_3C$ with variation in the temperature. The dissociation constants K_1 and K_2 being known at two (absolute) temperatures T_1 and T_2 respectively, the heat of dissociation can be calculated from the equation

$$H = R \frac{T_1 T_2}{T_2 - T_1} \ln \frac{K_2}{K_1}$$

where H represents the net increase in heat content of the system.

From the values of the dissociation constants for hexaphenylethane in benzene ($K \times 10^4 = 2.6$ at 13°C. , 7.84 at 30°C. , 18.8 at 43°C.), determined by measurements of the molecular extinction coefficients, Ziegler and Ewald¹⁷ obtained a value of 11.8 kcal. for the heat of dissociation. Practically the same value (10.5 – 12 kcal.) was obtained in nine different solvents. Similar results were obtained from the values of the equilibrium constants calculated from colorimetric data¹⁶ and magnetic susceptibility measurements.²³ By the substitution of six phenyl groups for the six hydrogen atoms of ethane, the carbon-carbon bond strength is reduced from about 70 – 80 kcal.²⁴ to 11.8 kcal., a decrease of about 10 – 11 kcal. for each phenyl group.

The rate of dissociation of hexaphenylethane is rapid, although it appears slow in comparison with the speed with which the free radicals react. If a reaction is studied in which the reagent reacts practically instantly with triphenylmethyl, then the speed of the over-all reaction will be a measure of the relatively slow dissociation process. Iodine, nitric oxide, and oxygen (in the presence of pyrogallol as an inhibitor of chain reactions involving the reaction of hexaphenylethane itself with the oxygen) have been employed.^{25, 26} With these reagents practically the same rate, corresponding to a unimolecular reaction $-\log(1 - Z) = kt/2.3$, where Z is the fraction of hexaphenylethane reacted in time t , and k is the specific reaction rate constant, was obtained. In chloroform at 0° , k was found to be equal to 0.21 . From this the "half-life" or period of half-change of hexaphenylethane can be calculated to be 3.3 minutes; that is, one-half of the hexaphenylethane dissociated in this

²³ Müller and Müller-Rodloff, *Ann.*, **521**, 89 (1935).

²⁴ Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y. (1940), gives a value 58.6 kcal. for the *average* energy of the carbon-carbon bond; this value does not necessarily represent the heat of dissociation of ethane into methyl radicals.

²⁵ Mithoff and Branch, *J. Am. Chem. Soc.*, **52**, 255 (1930).

²⁶ Ziegler, Orth, and Weber, *Ann.*, **504**, 131 (1933); Ziegler and Ewald, *Ann.*, **504**, 162 (1933).

period when the radicals were removed as fast as they were formed. At 10° in the same solvent the half-life was only 1 minute.

From the rates of dissociation and their temperature coefficients the heat of activation of the dissociation process can be calculated. While the energy of dissociation is concerned only with the initial and final states and tells to what extent dissociation occurs, the energy of activation involves the energy needed to break the bond and gives information as to how fast the reaction proceeds. From the value of k_1 (0.21 at 0° C.) and k_2 (0.72 at 10° C.) for hexaphenylethane in chloroform, the heat of activation can be calculated (using the same expression as for heat of dissociation) to be 19 kcal. Although the rate constants varied greatly in the nineteen different solvents which were used for the reactions, practically the same value for the heat of activation was obtained.

The heat of activation is larger than the heat of dissociation by about 8 kcal.; this difference represents the amount of activation energy required for two moles of triphenylmethyl to unite to form hexaphenylethane.

Theories of Dissociation. Numerous explanations have been advanced to account for the dissociation of hexaarylethanes into free radicals. Why does the substitution of six phenyl groups for the six hydrogen atoms of ethane, which is extremely stable and shows no signs of dissociation below 500°, cause the molecule to undergo dissociation at room temperature or below? According to one of the early views, the phenyl groups take up so much of the "affinity" of the central carbon atom that there is little tendency for the radical to combine with another similar molecule.

Kharasch²⁷ considered that the electronegativities (p. 1072) of the groups were of paramount importance in causing dissociation. According to him, substitution of three electronegative groups for the three hydrogen atoms of the methyl group results in a displacement of the valence electrons away from the central carbon atom, thus making the radical weakly electronegative. It was considered that two such weakly electronegative radicals should not form a stable compound. The greater the electronegativities of the substituting groups the larger the degree of dissociation of the ethane. Within certain limits there is a rough correspondence between the electronegativity of a group and its effectiveness in promoting dissociation, but there are also some striking differences.

According to another hypothesis the size and weight of the groups are especially responsible. In virtue of the steric hindrance offered by the large groups the two ethane carbon atoms are unable to approach

²⁷ Kharasch and Marker, *J. Am. Chem. Soc.*, **48**, 3130 (1926); Kharasch and Flenner *ibid.*, **54**, 674 (1932).

each other closely enough to form a normal carbon-carbon bond. In order to account for the greater effectiveness of the phenyl group in comparison with the cyclohexyl group in promoting dissociation, it was necessary to consider that unsaturation was essential. That unsaturation alone is not sufficient was indicated by Marvel's work on ethanes containing the highly unsaturated ethynyl groups. Even hexa-(*tert.*-butylethynyl)-ethane in which bulky unsaturated groups are present exhibited no dissociation.

At the present time it is perhaps generally considered that the dissociation of the hexaarylethanes is more or less adequately explained on the basis of resonance and steric hindrance. While most theories account for dissociation on the basis of a weakened carbon-carbon linkage, Pauling and Wheland²⁸ considered the strength of the bond in hexaarylethanes to be the same as that in ethane (70–80 kcal.). According to them, dissociation is due not to the weakness of the ethane linkage but to the stabilization of the free radicals as a result of resonance. In the triphenylmethyl radical there are more possibilities for resonance than exist for the triphenylmethyl group in the hexaphenylethane, for in addition to having the resonance of the group the radical can resonate among nine additional structures in which the unpaired electron is upon the *ortho* and *para* positions of the benzene rings (p. 1980). Resonance among these structures increases the resonance energy of the system (resulting in a lower energy content of the resultant hybrid structure), and this increase compensates for the energy required to break the carbon-carbon bond. With *p*-biphenyl or α -naphthyl groups attached to the central carbon atom the number of resonance possibilities is increased, and with a sufficient number of these groups present the extra resonance energy may amount to the energy of the carbon-carbon linkage.

Although the results of the calculations of the resonance effect are qualitative in nature, partly perhaps because of certain assumptions that must be made, such as a planar molecule, it is significant that the calculated values are of the right order of magnitude. Moreover, the calculations give the right order for the relative effectiveness of various groups in promoting dissociation, namely, α -naphthyl > *p*-biphenyl > β -naphthyl > phenyl. From similar considerations, Ingold²⁹ has predicted the following order for the groups in promoting radical stability: 9-phenanthryl > α -anthryl > α -naphthyl > β -naphthyl > *p*-biphenyl > *m*-biphenyl > phenyl. From the standpoint of testing Ingold's prediction in regard to the 9-phenanthryl group, it was unfortunate that the

²⁸ Pauling and Wheland, *J. Chem. Physics*, **1**, 362 (1933). See also Hückel, *Z. Physik* **83**, 632 (1933); Ingold, *Ann. Repts. Chem. Soc.*, **25**, 152 (1928).

²⁹ Ingold, *Trans. Faraday Soc.*, **30**, 52 (1934).

free radical 9-phenanthryldiphenylmethyl decomposed too rapidly to allow measurement to be made on it.³⁰

From a study of the heats of oxidation and hydrogenation of triphenylmethyl, Bent³¹ has concluded that the bond in hexaphenylethane is weaker than that in ethane by about 30 kcal., and he attributes the weakening effect to steric hindrance. As will be mentioned later, certain alkyl groups when attached to the central carbon atom are effective in promoting radical stability; thus, the *tert.*-butyl group is as effective in this respect as the phenyl group. This may be explained in terms of a steric effect or on the basis of resonance in the alkyl group as Wheland³² has done. The latter explanation might be used to explain the effect of *para*-substituted alkyl groups in promoting radical stability but would be inadequate to account for the much greater effect of the alkyl groups when situated in the *ortho* positions.²² In the latter case the steric effect is probably predominant.

Further investigations are desirable in order to determine the exact contribution made by resonance and by steric effects in promoting the dissociation of hexaarylethanes and to determine whether some other factor in addition to these is operative.

Preparation of the Free Radicals. More than a hundred compounds have been prepared, many only in solution, which dissociate into triarylmethyl radicals. Most of the compounds that have been isolated are colorless, or nearly so, in the solid state, and it is generally assumed that the solid compound is the hexaarylethane. A few free radicals themselves, notably tri-*p*-biphenylmethyl, phenyl- α -naphthyl-*p*-biphenylmethyl, and tri-*p*-nitrophenylmethyl, have been isolated in the form of colored crystals.

Three general methods have been employed to prepare solutions containing the triarylmethyls from which the hexaarylethane may be isolated: (1) by reaction of a triarylechloromethane with a metal; (2) by reduction of a triarylmethyl salt; (3) by abstraction of the metallic atom from the salts R_3CK .

1. The classical method of Gomberg, which is most frequently used, consists in abstracting the halogen from a triarylmethyl halide, usually the chloride. The triarylecarbinol can be prepared generally from a ketone and a Grignard reagent or from an ester and two moles of a Grignard reagent. The triarylechloromethane is formed by reaction of the triarylecarbinol with acetyl chloride or with dry hydrogen chloride. In this manner triarylechloromethanes containing substituted phenyl groups and different aryl groups can be prepared.

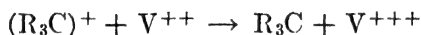
³⁰ Bachmann and Klotzel, *J. Org. Chem.*, **2**, 356 (1937).

³¹ Bent and Cuthbertson, *J. Am. Chem. Soc.*, **55**, 170 (1936).

³² Wheland, *J. Chem. Phys.*, **2**, 474 (1934).

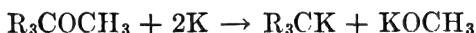
A benzene solution of the triarylchloromethane is shaken with mercury or "molecular" silver (prepared by electrolytic precipitation of the metal from silver chloride) at room temperature for several days.³³ Other metals such as zinc, copper (with heating), and sodium have been employed, the last also in liquid ammonia.³⁴ By concentrating the filtered, colored solution the hexaarylethane is obtained. Generally speaking, the essential conditions for the reaction are exclusion of all moisture in order to prevent hydrolysis of the halide, absence of oxygen, exclusion of acids, and protection from light. The reasons for these precautions will be clear from a study of the chemical properties of the triarylmethyls.

2. It is generally considered that the intense colors of solutions of triarylcarbinols in alcohol or acetic acid containing a mineral acid are due to the formation of ionizable halochromic salts, $R_3COH + HX \rightarrow (R_3C)^+ + X^- + H_2O$. The neutral free radical can be produced from the ion by means of certain soluble reducing agents as vanadous chloride and titanous chloride just as metals may be precipitated from solutions of their salts by suitable reducing agents.



As a rule the hexaarylethane precipitates out of the solution as it is formed by association of the free radical. By this reaction Conant and co-workers^{35, 36} have isolated certain hexaarylethanes, such as those containing dimethylamino groups, which are difficult or impossible to prepare by other methods.

3. The third method is generally employed when the chloride is not obtainable and has found its chief application in the preparation of free radicals other than the triarylmethyls. In this method the methyl ether of the carbinol is cleaved by metallic potassium to give the organopotassium derivative from which the potassium is abstracted by means of tetramethylethylene bromide³⁷ (ethylene dibromide tends to split off hydrogen bromide).



Chemical Properties. The triarylmethyls in solution differ widely in stability, the least stable being those with OH, OCH₃, NO₂, and N(CH₃)₂ groups. Some radicals retain their unsaturated character for months,

³³ Gomberg and Schoepfle, *J. Am. Chem. Soc.*, **39**, 1652 (1917).

³⁴ Kraus and Kawamura, *ibid.*, **45**, 2756 (1923).

³⁵ Conant and Sloan, *ibid.*, **47**, 572 (1925); Conant, Small, and Taylor, *ibid.*, **47**, 1959 (1925).

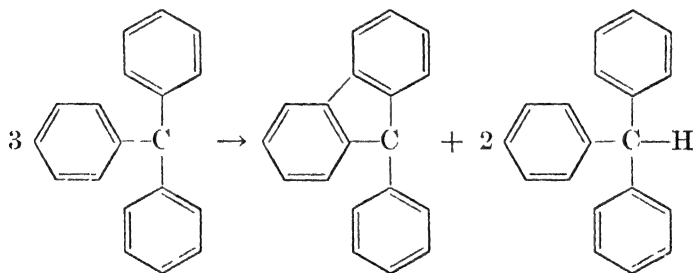
³⁶ Conant and Bigelow, *ibid.*, **53**, 676 (1931).

³⁷ Ziegler and Schnell, *Ann.*, **437**, 227 (1924).

others for only a few hours, and some decompose spontaneously in a few minutes. This instability makes it extremely difficult to work with certain free radicals.

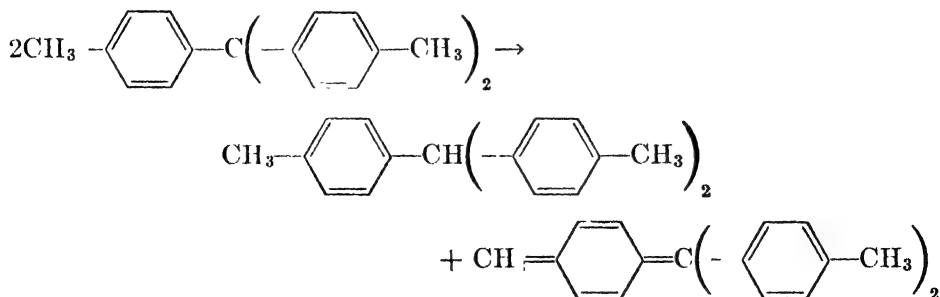
For the most part the products of the decomposition of the radicals are not known, but sometimes it has been possible to determine the nature of the reactions that take place from the products which have been isolated. Polymerization, reduction, and oxidation are some of the reactions that take place, often spontaneously. Certain of these reactions are hastened or initiated by light, heat, or acids. Thermal decomposition of triphenylmethyl in boiling xylene yields highly colored uncrystallizable oils as the chief product in addition to a small amount of triphenylmethane.

Disproportionation and Irreversible Dimerization. One of the characteristic reactions undergone by all free radicals is disproportionation, in which one molecule of the radical becomes reduced at the expense of another molecule which becomes oxidized. This reaction with the triarylmethyls is promoted especially by light. If a solution of triphenylmethyl is exposed to sunlight, the yellow color of the solution gradually fades as disproportionation takes place.



The products are triphenylmethane and 9-phenylfluorene (which at room temperature associates completely to the hexaarylethane).

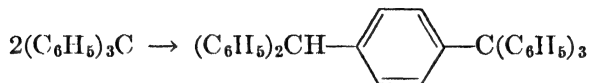
Tri-*p*-tolylmethyl rapidly disproportionates to yield a mixture of tri-*p*-tolylmethane and a quinoid compound which undergoes polymerization.³⁸



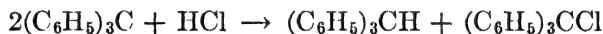
³⁸ Marvel, Rieger, and Mueller, *J. Am. Chem. Soc.*, **61**, 2769 (1939).

This reaction appears to be characteristic of hexaarylethanes containing a *para*-substituted alkyl group which has a hydrogen atom on the α carbon atom.

Another characteristic reaction of triarylmethyl radicals is the irreversible dimerization to an isomer of the hexaarylethane; with triphenylmethyl the product is *p*-benzohydryltetraphenylmethane.

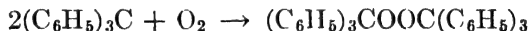


This reaction takes place especially in the presence of mineral acids, even traces of the acid sufficing to produce the change. Treatment of a benzene solution of triphenylmethyl with dry hydrogen chloride or even shaking the solution with an aqueous concentrated solution of hydrochloric acid converts the radical to the dimer. To a slight extent the triphenylmethyl is converted to a mixture of equal parts of triphenylmethane and triphenylchloromethane.



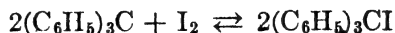
This type of reaction is the principal one occurring with some radicals, for example diphenyl- α -naphthylmethyl.

Addition Reactions. One of the most remarkable properties of the triarylmethyl radicals is the rapid absorption of atmospheric oxygen to form colorless triarylmethyl peroxides.³⁹



If the solution of the free radical is shaken with excess of oxygen, the absorption of oxygen is complete in a minute or two at room temperature. Since the volume of oxygen that is absorbed corresponds roughly to the amount demanded by the equation, the reaction has been used to determine the purity of a given sample of triarylmethyl. The peroxides are usually crystalline compounds that can be isolated from the reaction mixture. Even when the free radical decomposes rapidly, the peroxides can often be obtained; invariably this can be done by shaking the triarylmethyl halide with silver in the presence of oxygen. The reaction with oxygen serves as a convenient test for triarylmethyl radicals.

Another striking reaction of triarylmethyls is the combination with iodine at room temperature. The iodine adds to the carbon atom and a triarylmethyl iodide is formed.



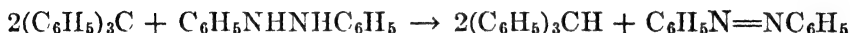
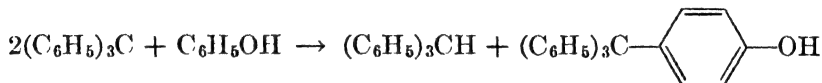
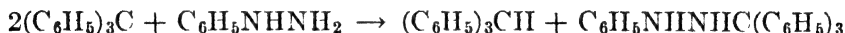
³⁹ Gomberg and Cone, *Ber.*, **37**, 3538 (1904).

The reaction is reversible, and the equilibrium that is reached varies with the particular compound, but usually corresponds to 60–80 per cent formation of the triarylmethyl iodide in 2–3 per cent solutions.

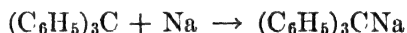
Triphenylmethyl is reduced by hydrogen although not rapidly; in the presence of platinum black, hydrogen is absorbed and triphenylmethane is formed. The same product results when the radical is treated with zinc and acetic acid.



Triphenylmethyl is capable of abstracting hydrogen atoms from phenylhydrazine, phenol, and hydrazobenzene.



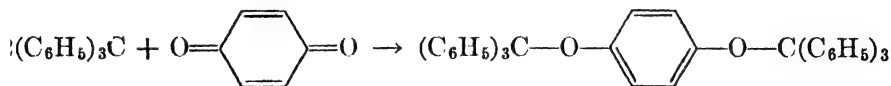
Sodium, in the form of sodium powder or amalgam, adds to triphenylmethyl in ether-benzene or in liquid ammonia and gives the intensely red triphenylmethylnsodium



The Grignard reagent triphenylmethylmagnesium bromide can be obtained in quantitative yield by reaction of triphenylmethyl with a mixture of magnesium and magnesium bromide in anhydrous ether and benzene.⁴⁰



Two molecules of triphenylmethyl add to one of quinone and form the ditriphenylmethyl ether of hydroquinone.

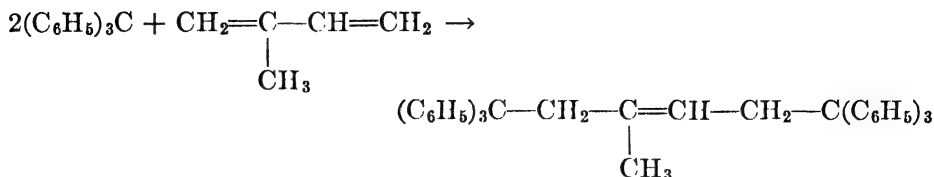


Similar to this reaction is the addition of triphenylmethyl to unsaturated hydrocarbons and related compounds.⁴¹ With isoprene, for

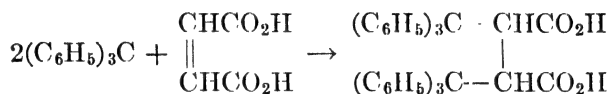
⁴⁰ Gomberg and Bachmann, *J. Am. Chem. Soc.*, **52**, 2455 (1930).

⁴¹ Conant and Scherp, *ibid.*, **53**, 1941 (1931).

example, 1,4-addition of the free radical takes place and 1,1,1,6,6,6-hexaphenyl-3-methylhexene-3 is formed.



With maleic acid ditriphenylmethylsuccinic acid is produced.

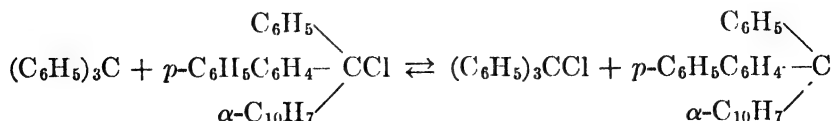


Nitric oxide is absorbed by triphenylmethyl; the initial product is nitrosotriphenylmethane, $(\text{C}_6\text{H}_5)_3\text{CNO}$, which undergoes further reaction to undetermined products. Nitrogen dioxide is likewise absorbed by the free radical; the products are triphenylnitromethane and triphenylmethyl nitrite. Sulfur adds to triphenylmethyl, and polysulfides are formed.

The triarylmethyls exhibit a pronounced tendency to form molecular addition complexes with a variety of liquids. Addition complexes have been obtained from triphenylmethyl and aldehydes, ketones, esters, nitriles, chloroform, ethers, benzene, and even saturated hydrocarbons as heptane, decane, and cyclohexane.⁴² The addition compounds usually lose the solvent at 50–100°, but some are remarkably stable.

Because of the extraordinary tendency to undergo addition reactions, triphenylmethyl has found application as a reagent for the detection of other free radicals, and to "capture" short-lived free radicals which are formed as intermediates in certain chemical reactions.

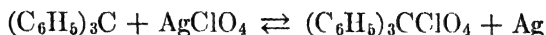
Reactions with Triarylmethyl Halides and Inorganic Salts. The triarylmethyls possess a number of properties which find their counterpart in the behavior of metals. Just as one metal can displace another from its salt, so can one triarylmethyl displace another from its triarylmethyl halide. Thus, addition of a yellow solution of triphenylmethyl to a colorless solution of phenyl-*p*-biphenyl- α -naphthylchloromethane evokes the deep brown color of phenyl-*p*-biphenyl- α -naphthylmethyl.⁴³ The following reaction proceeds until equilibrium is attained:



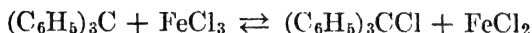
⁴² Gomberg, *ibid.*, **36**, 1144 (1914); *Chem. Rev.* **1**, 91 (1924); **2**, 310 (1925).

⁴³ Schlenk and Herzenstein, *Ann.*, **394**, 199 (1912).

Like metals, the triarylmethyls are capable of reducing certain inorganic salts.⁴⁴ Silver perchlorate and other silver salts are reduced by triphenylmethyl to metallic silver.

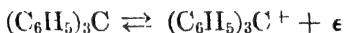


Similarly, mercury, platinum, and auric salts are reduced to the corresponding metal by the free radical. Ferric chloride is reduced to ferrous chloride.



The reverse of this type of reaction, namely, the reduction of the triarylmethyl salt to the free radical, has already been discussed as a method of preparing the radicals. Conant and co-workers³⁵ found that a mixture of a radical and its halochromic salt possesses a definite potential analogous to that of a metal in contact with a solution of its salt. They determined the single-electrode potentials of several radicals at varying concentrations of hydrogen ion.

Solutions of triarylmethyl halides in liquid sulfur dioxide are good conductors of the electric current; the carriers appear to be the triarylmethyl cation and the chloride ion which are produced by ionization of the halide, $\text{R}_3\text{CCl} \rightleftharpoons (\text{R}_3\text{C})^+ + \text{Cl}^-$. On electrolysis of the solution the electrically neutral radical is formed at the cathode. Solutions of the free radicals in sulfur dioxide also conduct the current, a remarkable property for a hydrocarbon; no conduction is observed in benzene or in nitrobenzene. The triphenylmethyl radical gives up its unpaired electron to the sulfur dioxide, and triphenylmethyl cations are formed, a process analogous to that which takes place when sodium is dissolved in liquid ammonia.



The cation and the solvated electron, and not the free radical, are the true conductors. The absorption curve for a solution of triphenylmethyl in sulfur dioxide is similar to that for a solution of triphenylmethyl bromide in the same solvent, and in dilute solutions the amount of triphenylmethyl cation is the same from both sources, radical and halide.⁴⁵ The absorption curve for triphenylmethyl in ether, in which the radical is not ionized, is different from the curves obtained for the triphenylmethyl cation.

The free radicals may be characterized as amphoteric in nature inasmuch as the triarylcarnibols R_3COH exhibit baselike properties in their ability to form ionizable halochromic salts with mineral acids and the

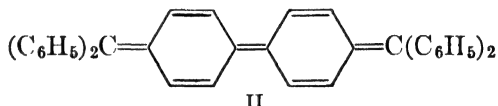
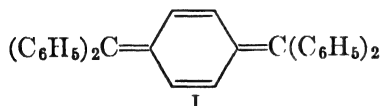
⁴⁴ Gomberg and Gamrath, unpublished results.

⁴⁵ Anderson, *J. Am. Chem. Soc.*, **57**, 1673 (1935).

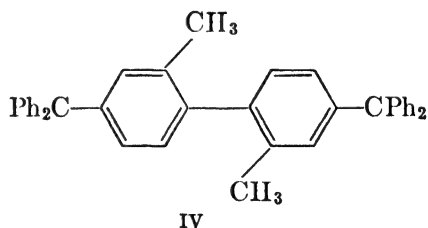
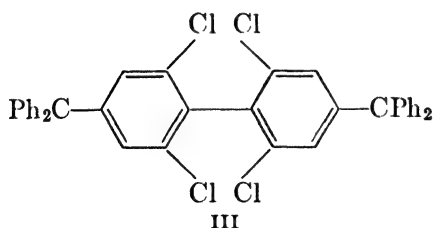
corresponding hydrides R_3CH are weakly acidic, forming sodium derivatives R_3CNa , which yield triarylmethyl anions.

Biradicals

A number of compounds known as biradicals have been prepared which appear to contain two carbon atoms each linked to only three groups. A quinoid structure has been assigned to the intensely colored hydrocarbons of the type of *p,p'*-phenylenebis(diphenylmethyl) (I) because of the relative stability of solutions of the hydrocarbons to oxygen. Irradiated solutions, however, lose their color in the presence of oxygen, and it has been suggested that the biradical is formed under the influence of light.⁴⁶ Although some have considered that the violet-colored solid *p,p'*-biphenylenebis(diphenylmethyl) (II), which in solution rapidly



absorbs oxygen, exists entirely in the biradical form, measurements of its paramagnetic susceptibility have shown that the compound is practically entirely (at least 99 per cent) in the quinoid form. In general it appears that the quinoid rather than the biradical structure is assumed whenever the former state is possible. In order to prevent the formation of the quinoid form Müller and Neuhoﬀ⁴⁷ and Theilacker and Ozegowski⁴⁸ introduced large groups into the *ortho* positions of the biphenyl ring; since the coplanar structure is not possible, the quinoid form cannot be taken. As a result the compounds which they prepared exist in part as the biradicals III and IV.



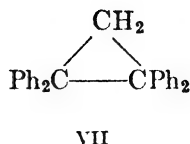
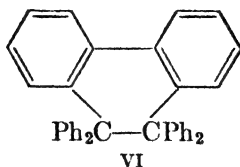
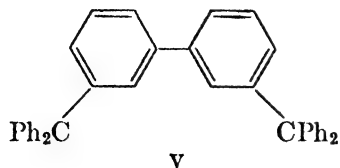
In the *meta* derivative (V), in which quinoidation is not possible, about 6 per cent of the biradical is present in a benzene solution at 74°.

⁴⁶ Schönberg, *Trans. Faraday Soc.*, **32**, 514 (1936).

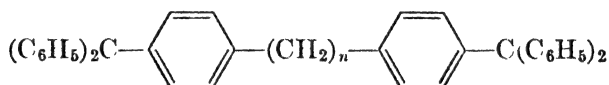
⁴⁷ Müller and Neuhoﬀ, *Ber.*, **72**, 2063 (1939).

⁴⁸ Theilacker and Ozegowski, *Ber.*, **73**, 33, 898 (1940).

The corresponding *ortho* compound, 9,9,10,10-tetraphenyldihydronaphthalene (VI), shows no signs of dissociation.

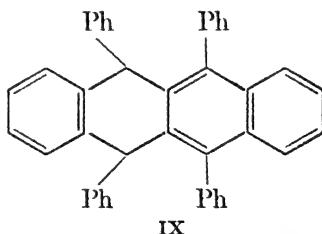
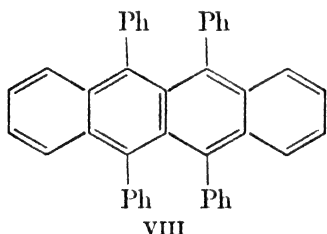


Wittig and Leo⁴⁹ have prepared 1,1,2,2-tetraphenylcyclopropane (VII) in order to determine whether the ring strain would aid in rupturing the bond between the two carbon atoms holding the aryl groups. The compound, however, proved to be colorless and stable. They have also prepared compounds of the type



where $n = 1, 2, 3$, and 4 . Intramolecular union of the two terminal valences is not possible when n is 1 or 2, and the biradicals that are formed show a broad absorption band like that of tri-*p*-biphenylmethyl. When n is 3 or 4, union of the valences is possible and the absorption band of the biradicals resembles that of triphenylmethyl.

The interesting red hydrocarbon 5,6,11,12-tetraphenylnaphthacene (VIII) of Moureu and Dufraisse⁵⁰ absorbs oxygen when irradiated, and it has been assumed that the light energy transforms the ordinary form of the molecule into the biradical (possibly IX), but this has not been



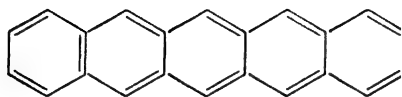
confirmed by magnetic measurements.⁵¹ Similarly 2,3,6,7-dibenzanthracene, a violet-colored hydrocarbon, exists completely in the quinoid form (X) both in solution and in the solid state contrary to the view of Clar,⁵² who believed it to be entirely in the biradical form.

⁴⁹ Wittig and Leo, *Ber.*, **61**, 854 (1928); **62**, 1405 (1929).

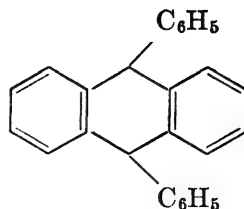
⁵⁰ Moureu and Dufraisse, *Bull. soc. chim.*, [4] **53**, 789 (1933); a review of the chemistry of the rubenes. Dufraisse and Velluz, *Compt. rend.*, **201**, 1394 (1935); Allen and Gilman, *J. Am. Chem. Soc.*, **58**, 937 (1936).

⁵¹ Müller and Müller-Rodloff, *Ann.*, **517**, 134 (1935).

⁵² Clar, *Ber.*, **65**, 503 (1932).



X



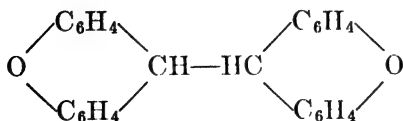
XI

When a solution of 9,10-diphenylanthracene is heated a color develops, which fades when the solution is cooled. Ingold and Marshall⁵³ ascribed the color to the biradical XI, but Dufraisse and Houpillart⁵⁴ believe that the color arises simply from a general modification of the light absorption by 9,10-diphenylanthracene with increased temperature.

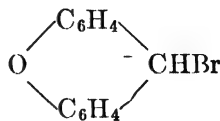
Diarylmethyls

sym.-Tetraarylethanes. The successful demonstration that compounds can be prepared in which a carbon atom is linked to only three groups naturally encouraged investigation to determine whether the three groups needed to be aryl groups. The two tetraphenylethanes can be distilled (b. p. 280°) without decomposition, and no evidence of dissociation has been detected in *sym.*-tetra-*p*-biphenylethane. In harmony with these results is the fact that one cannot prepare a solution containing appreciable amounts of diphenylmethyl radicals, $(\text{C}_6\text{H}_5)_2\text{CH}\cdot$. As will be shown in a later section, there is evidence that diphenylmethyl radicals are formed by reaction of diphenylbromomethane with silver, but these rapidly associate completely to form *sym.*-tetraphenylethane. Recently Nauta and Wuis⁵⁵ reported that the violet-red solution which is formed by the action of silver on dimesitylbromomethane in benzene probably contains the free dimesitylmethyl radical, but further evidence is required before this view can be accepted.

In the tetraarylethanes and other compounds that will be met with later we encounter what might be termed borderline cases in which it is sometimes difficult to distinguish whether a slight dissociation occurs or whether the compounds simply possess a weakened ethane linkage. Thus, bixanthyl (XII) does not appear to dissociate into free xanthyl



XII



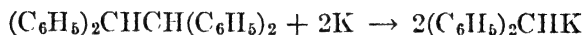
XIII

⁵³ Ingold and Marshall, *J. Chem. Soc.*, 3080 (1926).

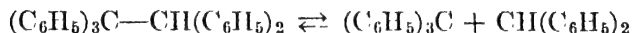
⁵⁴ Dufraisse and Houpillart, *Bull. soc. chim.*, [5] **5**, 1628 (1938).

⁵⁵ Nauta and Wuis, *Rec. trav. chim.*, **57**, 41 (1938).

radicals, yet the compound reacts with bromine to give two molecules of xanthyl bromide (XIII), and a solution of bixanthyl absorbs oxygen at 150° and gives xanthone. That the ethane linkage in the two tetraphenylethanes is weakened by the four aryl groups is shown by the cleavage of the bond by metallic potassium at room temperature.



Pentaarylethanes. The pentaarylethanes are colorless solids which give colorless solutions at room temperature.⁵⁶ The solutions are relatively stable to air at room temperature, but at 100° oxygen is absorbed rapidly to give the unsymmetrical triarylmethyldiarylmethylperoxide $\text{R}_3\text{COOCHIR}_2$ as the chief product in addition to a small amount of triarylmethylperoxide. From a study of the rate of oxygen absorption at 80–100° it was established that pentaphenylethane in solution undergoes reversible dissociation into triphenylmethyl and diphenylmethyl radicals.⁵⁷



The rate-controlling step was found to be a unimolecular reaction in agreement with that demanded by the dissociation process. The degree of dissociation is extremely slight, as is evident from the fact that a solution of pentaphenylethane in *o*-dichlorobenzene is colorless even at 95°, yet dissociation at this temperature is rapid, the "half-life" being 9 minutes, as measured by the rate of reaction with oxygen and with iodine. At 100° the half-life of pentaphenylethane is approximately the same as that of hexaphenylethane at 0° in toluene, namely, about 5 minutes. The heat of activation of the dissociation process was found to be about 28 kcal., which is about 8–9 kcal. higher than that of hexaphenylethane.

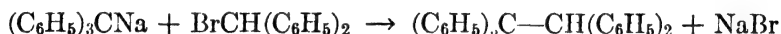
The behavior of solutions of the pentaarylethanes can be readily interpreted in terms of the reversible dissociation of the hydrocarbons into free radicals. When a solution of a pentaarylethane is heated a temperature is reached at which the color of the triarylmethyl radical appears; this radical becomes visible when a sufficient number of the diarylmethyl radicals have been removed from the equilibrium (by irreversible association to *sym*.-tetraarylethane). The color is not removed when the solution is cooled, but can be discharged by oxygen or iodine. The temperature (70–105° for most of them) at which the color appears varies with the groups present in the pentaarylethane

⁵⁶ Bachmann, *J. Am. Chem. Soc.*, **55**, 2135 (1933).

⁵⁷ Bachmann and Wiselogle, *J. Org. Chem.*, **1**, 354 (1936); Bachmann and Osborn, *ibid.*, **5**, 29 (1940).

The groups that especially promote dissociation of hexaarylethanes, α -naphthyl, *p*-biphenyl, and *p*-anisyl, have a similar effect in the pentaarylethanes. Continued heating at 150–200°, at which temperature the triarylmethyl radicals are decomposed, leads to complete decomposition of the pentaarylethane with formation of large amounts of the *sym*-tetraarylethane. The rapid reaction of pentaphenylethane with bromine at 100° to give triphenylbromomethane and diphenylbromomethane and the reduction of pentaarylethanes by phosphorus and hydrogen iodide in acetic acid (118°) to triarylmethanes and diarylmethanes are readily explained on the basis of the intermediate formation of the free radicals.

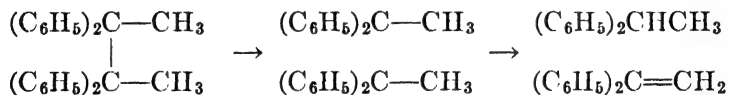
The pentaarylethanes are easily obtainable through reaction of a diarylmethyl halide and a triarylmethylsodium or in some cases a triarylmethylmagnesium bromide.



An interesting synthesis of pentaphenylethane involving the "capture" of diphenylmethyl radicals by triphenylmethyl radicals is described in the discussion of mechanisms of reactions.

Diarylalkylmethylys

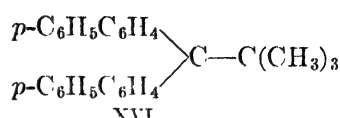
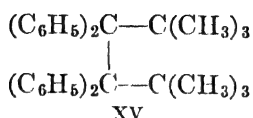
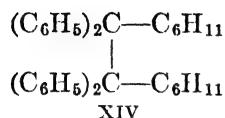
***sym*-Tetraaryldialkylethanes.** Substitution of two alkyl groups for the two hydrogen atoms of *sym*-tetraphenylethane weakens the ethane bond to such an extent that the compounds are thermally unstable and may dissociate. *sym*-Tetraphenyldimethylethane and *sym*-tetraphenyldiethylethane decompose spontaneously in solution, the latter hydrocarbon more easily than the former. In this decomposition *sym*-tetraphenyldimethylethane gives 1,1-diphenylethane and 1,1-diphenylethylene, and one may suppose that radicals are formed which quickly undergo disproportionation.



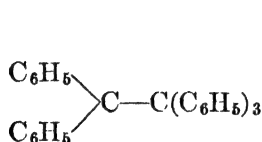
The *sym*-tetraaryldialkylethanes were prepared from the methyl ethers of the diarylalkylcarbinols by method 3 described under the preparation of triarylmethyls (p. 595). This method was employed because the diarylalkylchloromethanes are unstable and lose hydrogen chloride to yield olefins.

Secondary and tertiary alkyl groups have a greater influence than primary groups in weakening the ethane linkage. Thus, *sym*-tetraphenyldicyclohexylethane (XIV) in solution absorbs oxygen and gives a peroxide, as does *sym*-diphenyltetracyclohexylethane, although no evi-

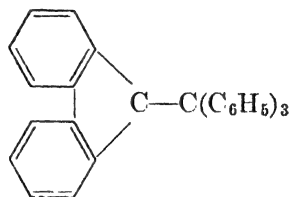
dence of dissociation of the latter hydrocarbon has been obtained by physical methods. *sym.*-Tetraphenyl-di-*tert.*-butylethane (XV) appears to dissociate into radicals when its solution is heated above 50°, and *sym.*-tetra-*p*-biphenyl-di-*tert.*-butylethane is 74 per cent dissociated in dilute solution into orange-red di-*p*-biphenyl-*tert.*-butylmethyl radicals (XVI).⁵⁸



Pentaarylethyls. The tertiary triphenylmethyl group seems to be more effective than any aryl group in promoting dissociation. Schlenk and Mark⁵⁹ have reported that the yellow pentaphenylethyl (XVII) and the violet 9-(triphenylmethyl)-fluoryl (XVIII) are unimolecular free



XVII

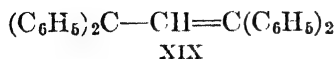


XVIII

radicals both in solution and in the solid state. The preparation of pentaphenylethyl was carried out in the following manner.



Tetraarylallyls. The unsaturated β, β -diphenylvinyl group $(\text{C}_6\text{H}_5)_2\text{C}=\text{CH}-$ is especially effective in promoting dissociation. Free radicals have been prepared in which the phenyl groups of triphenylmethyl have been replaced by one, two, and three of these unsaturated groups.⁶⁰ Even 1,1,3,3-tetraphenylallyl (XIX), which contains only one β, β -diphenylvinyl group, is present to the extent of 80 per cent in equilibrium with the bimolecular form in a 2 per cent benzene solution at 5°, and 1,1-di-*p*-anisyl-3,3-diphenylallyl (XX) is completely unasso-



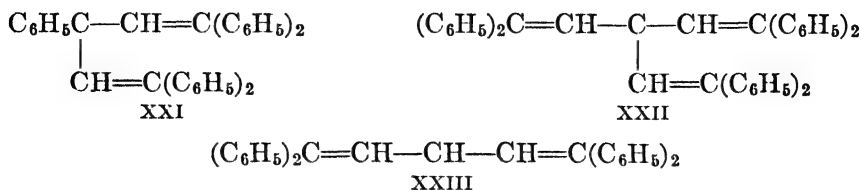
ciated under the same conditions. Phenyl-di-(β, β -diphenylvinyl)-methyl

⁵⁸ Conant and Schultz, *J. Am. Chem. Soc.*, **55**, 2098 (1933).

⁵⁹ Schlenk and Mark, *Ber.*, **55**, 2285 (1922).

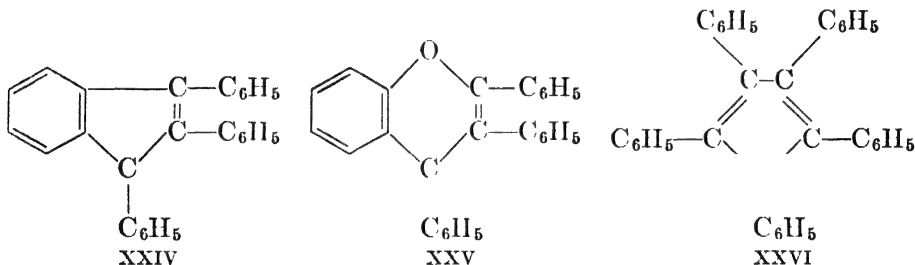
⁶⁰ Ziegler, *Ann.*, **434**, 34 (1923); Wittig and Obermann, *Ber.*, **68**, 2214 (1935); Wittig and Kosack, *Ann.*, **529**, 167 (1937).

(XXI) and tri-(β,β -diphenylvinyl)-methyl (XXII) (which forms black crystals) likewise appear to be unimolecular free radicals.

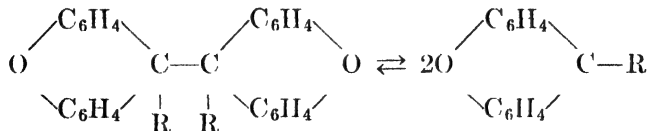


The radical di-(β,β -diphenylvinyl)-methyl (XXIII) has only two of the unsaturated groups in addition to a hydrogen atom attached to the central carbon atom. In these compounds the unpaired electron can shift to a number of different carbon atoms other than those in the ring. Attempts to prepare hexa- β -styrylethane and di- β -styryltetraphenylethane were unsuccessful; only stable isomeric hydrocarbons were obtained, presumably through rearrangement.⁶¹

Kohler⁶² was actually the first to observe the influence of the substituted vinyl group on radical formation. By removing the halogen atom from 1,2,3-triphenylindyl bromide by means of a metal he obtained the 1,2,3-triphenylindyl radical (XXIV). Closely related are 2,3,4-triphenylchromenyl (XXV) and pentaphenylcyclopentadienyl (XXVI) prepared by Ziegler. The last-mentioned radical, which has a beautifully symmetrical structure, does not associate to the bimolecular form.⁶³



9,9'-Dialkylbixanthyls. Conant⁶⁴ has summarized the effectiveness of various groups R in promoting dissociation in the substituted bi-



xanthyl molecule by placing them in three classes as follows.

⁶¹ Marvel, Mueller, and Peppel, *J. Am. Chem. Soc.*, **60**, 410 (1938).

⁶² Kohler, *Am. Chem. J.*, **40**, 217 (1908).

⁶³ Müller and Müller-Rodloff, *Ber.*, **69**, 665 (1936).

⁶⁴ Conant, Small, and Sloan, *J. Am. Chem. Soc.*, **48**, 1743 (1926).

Class I: cyclohexyl, isopropyl, *sec.*-butyl.

Class II: benzyl, *p*-chlorobenzyl, *pri.*-isobutyl, α -naphthylmethyl.

Class III: methyl, ethyl, *n*-butyl, *n*-hexyl, isoamyl, phenylethyl.

The substituted bixanthyls which contain groups from Class I as R give highly colored solutions at 25°; the colors become deeper when the solutions are warmed and fainter at low temperatures. The substances are unstable, and at temperatures above 60–70° the colors of the solutions disappear rapidly, probably through disproportionation of the free radicals. Solutions of the compounds absorb oxygen almost instantly at room temperature and usually give crystalline peroxides.

Solutions of bixanthyls containing groups of Class II become colored only when warmed to 80–100°. Even the colorless solutions absorb oxygen very rapidly at room temperature.

The primary groups (Class III) are least effective in weakening the ethane linkage; solutions of bixanthyls containing these groups become colored only when heated to about 140°. All these compounds absorb oxygen very slowly at room temperature. It has been shown that even in the colorless solution there exists a slight dissociation into alkylxanthyl radicals.⁶⁵

Conant⁶⁶ has evaluated the effect of various alkyl and aryl groups in decreasing the heat of dissociation of the ethane linkage. The decrease in kilocalories caused by the replacement of a single hydrogen of ethane was calculated to be: methyl, ethyl, 5; *n*-butyl, 6; benzyl, 7; biphenylene/2, 9; isopropyl, *tert.*-butyl, phenyl, 11; xanthyl/2, 11.5; *p*-anisyl, β -naphthyl, 12; α -naphthyl, 13.

Bent⁶⁷ has studied the addition of sodium to free radicals containing carbon linked to three groups, $R + Na = R^- + Na^+$. When the organosodium compound is shaken with mercury the reaction partially reverses, and from the equilibrium data the free energy change (p. 1794) of the reaction was obtained. It was found that the electron affinity of the free radicals was nearly the same (16–20 kcal.) for all of them. From the value of the free energy Bent calculated the heat of dissociation of dibenzylbixanthyl and diphenylbixanthyl to be 16–17 kcal., in agreement with the values obtained by Conant.

A rough comparison of the relative reactivity of certain substituted ethanes can be obtained by the use of liquid sodium-potassium alloy (2 : 5) and the liquid 40 per cent and 1 per cent sodium amalgams as is shown in Table IV.

⁶⁵ Conant and Evans, *ibid.*, **51**, 1925 (1929).

⁶⁶ Conant, *J. Chem. Phys.*, **1**, 427 (1933).

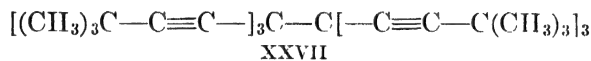
⁶⁷ Bent, *J. Am. Chem. Soc.*, **53**, 1786 (1931); Bent and Ebers, *ibid.*, **57**, 1242 (1935).

TABLE IV
CLEAVAGE OF SUBSTITUTED ETHANES BY ALKALI METALS

| Substance | Na-K | Na-Hg 40% | Na-Hg 1% |
|---------------------------------------|------|--------------|-------------|
| Hexaphenylethane..... | + | + | + |
| Di- <i>pri.</i> -alkylbixanthyIs..... | + | + | — |
| Bixanthyl..... | + | — | — |
| Tetraphenylethane | + | — | — |
| Bibenzyl..... | + | — | — |

A plus sign indicates appreciable cleavage in 5 minutes.

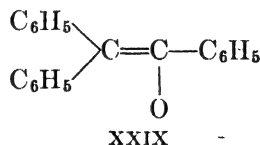
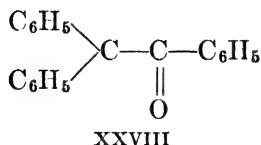
Aryl-(alkylethynyl)-ethanes. In order to determine whether unsaturation in groups is an important factor in promoting dissociation, Marvel⁶⁸ has prepared a large number of ethanes containing aliphatic acetylenic groups. An interesting member of the series is hexa-(*tert.*-butylethynyl)-ethane (XXVII). Some of the hydrocarbons absorbed oxygen, and all



of them were cleaved by the action of alkali metals. Many of them were extremely unstable, decomposing or rearranging to other products even at low temperatures. Although in no instance was direct proof obtained that dissociation into radicals took place, the intermediate formation of free radicals appeared to be responsible for some of the rearrangements undergone by these compounds.

Diarylacylmethyls

***sym.*-Tetraphenyldibenzoylthane.** This compound behaves as though it dissociated into free radicals.⁶⁹ Although it was expected that the compound would dissociate into diphenylbenzoylmethyl radicals



(XXVIII), the reactions of the free radical are better explained in terms of the mesomeric form (XXIX). Thus, the free radical does not react

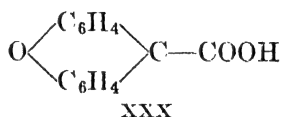
⁶⁸ Davis and Marvel, *ibid.*, **53**, 3840 (1931); Salzberg and Marvel, *ibid.*, **50**, 1737, 2840 (1928).

⁶⁹ Löwenbein and Schuster, *Ann.*, **481**, 106 (1930).

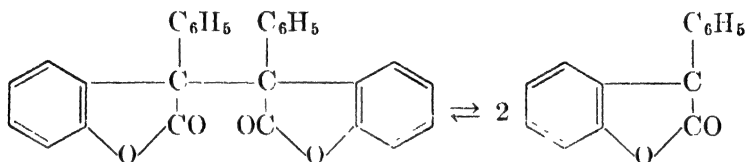
with bromine and it adds sodium to form the sodium salt of triphenylvinyl alcohol $(\text{C}_6\text{H}_5)_2\text{C}=\text{C}(\text{ONa})(\text{C}_6\text{H}_5)$.

Diarylcarboxymethyls

Bixanthyl-9,9'-dicarboxylic Acid. A solution of this acid or its dimethyl ester in ethyl benzoate becomes colored when heated to about $105\text{--}115^\circ$, and the color disappears when the solution is cooled.⁷⁰ In the process the free radicals 9-carboxyxanthyl (XXX) (or 9-carbomethoxyxanthyl) are formed. Towards oxygen the compounds are much less reactive than the least reactive of the 9,9'-dialkylbixanthyls.

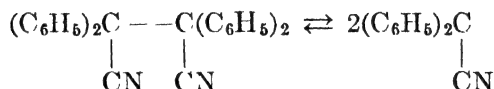


Bislactones of *sym.*-Diaryldi-(*o*-hydroxyaryl)-succinic Acids. The bislactone of *sym.*-diphenyldi-(*o*-hydroxyphenyl)-succinic acid dissociates to the extent of 50 per cent into free radicals in a hot dilute toluene solution.



Certain substituted lactones of this type appear to dissociate completely.⁷¹

Tetraarylsuccinonitriles. A solution of tetraphenylsuccinonitrile becomes colored when heated to 140° , and a solution of tetra-*p*-anisylsuccinonitrile exhibits a color at $60\text{--}80^\circ$ in virtue of the free diarylcyanomethyl radicals which are formed.⁷²



Solutions of the compounds absorb oxygen very slowly and react with nitrogen dioxide and with phenylhydrazine.

⁷⁰ Conant and Garvey, Jr., *J. Am. Chem. Soc.*, **49**, 2080 (1927).

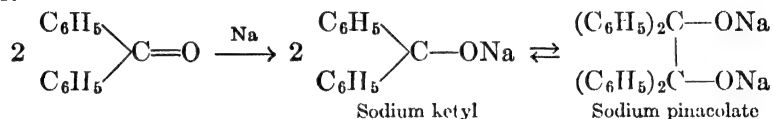
⁷¹ Löwenbein and Folberth, *Ber.*, **58**, 610 (1925).

⁷² Löwenbein and Gagarin, *Ber.*, **58**, 2643 (1925); Wittig and Petri, *Ann.* **513** 26 (1934); Wittig and Pockels, *Ber.*, **69**, 790 (1936).

Diarylhydroxymethyls

At 150–200° benzopinacol (tetraphenylethylene glycol) and other aromatic pinacols $R_2(OH)C-C(OH)R_2$ decompose with cleavage of the ethane linkage to give a mixture of the ketone R_2CO and the hydrol R_2CHOH . Although this reaction is interpreted conveniently in terms of an intermediate formation of free diarylhydroxymethyl radicals, no conclusive evidence has been obtained to show that pinacols dissociate into free radicals. Dissociation into colored free radicals occurs when the hydroxyl hydrogen atoms of the pinacol are replaced by metals.

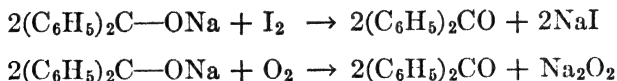
Metal Ketyls. In 1891 Beckmann and Paul observed that aromatic ketones react with metallic sodium in anhydrous ether to give deeply colored derivatives. Twenty years later, Schlenk and co-workers⁷³ showed that the colored compounds were free radicals of the type R_2C-ONa , formed by addition of an atom of sodium to a molecule of ketone.



Similar metal ketyls, as the radicals were named, are formed by reaction of aromatic ketones with potassium, lithium, cesium, and rubidium.

Although at first it was thought that the sodium ketyls are unimolecular radicals, it was shown later that association to the sodium pinacolate does take place.^{74, 75} The effect of solvent on the position of equilibrium was shown by measurements of the magnetic susceptibilities of the solutions. It was found that the sodium salts of benzopinacol and of *sym*.-4,4'-diphenylbenzopinacol are less than 1 per cent dissociated in benzene,⁷⁵ but in dioxane the potassium salt of the last-named pinacol is 85 per cent dissociated in the concentrations employed.⁷⁶

The sodium pinacolates dissociate rapidly into the sodium ketyl radicals. These radicals react rapidly with iodine and with oxygen; in both reactions the principal product is the ketone.



If dilute acid is employed for hydrolysis of the equilibrium mixtures in ether and benzene, nearly quantitative yields of the pinacols are ob-

⁷³ Schlenk and Thal, *Ber.*, **46**, 2840 (1913).

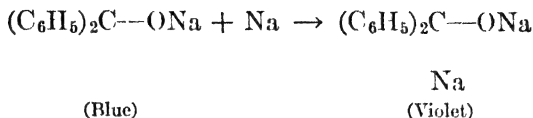
⁷⁴ Bachmann, *J. Am. Chem. Soc.*, **55**, 1179 (1933).

⁷⁵ Doescher and Wheland, *ibid.*, **56**, 2011 (1934).

⁷⁶ Sugden, *Trans. Faraday Soc.*, **30**, 18 (1934); Allen and Sugden, *J. Chem. Soc.*, 440 (1936).

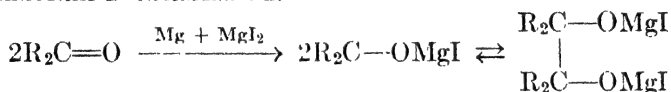
tained,⁷⁴ but with water alone a mixture of equal parts of ketone and hydrol is formed, presumably through cleavage by alkali of the pinacol initially formed.

When treated with an excess of sodium or 40 per cent sodium amalgam, the metal ketyls form intensely colored disodium derivatives of the ketones.



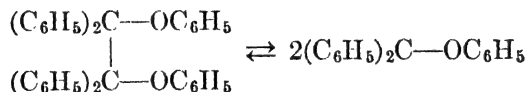
Sodium ketyls of the aliphatic and mixed aliphatic-aromatic series have been prepared. Branched aliphatic groups favor the formation of these ketyls. Thus, di-*tert.*-butyl ketone reacts with sodium to give a deep red sodium ketyl which slowly passes into the dimeric form. Crystalline sodium ketyls were obtained from ω -trialkylacetophenones and sodium.⁷⁷

Aromatic ketones react rapidly with a mixture of magnesium and magnesium iodide (which behaves like the equilibrium mixture, $\text{Mg} + \text{MgI}_2 \rightleftharpoons 2\text{MgI}$) in ether and benzene; colored iodomagnesium ketyls are formed by addition of MgI to the carbonyl group. These iodomagnesium ketyls quickly associate to colorless iodomagnesium pinacولات until equilibrium is established.⁷⁸



Hydrolysis of the mixtures usually gives nearly quantitative yields of pinacols. Like the sodium ketyls the iodomagnesium ketyls yield the ketone when they react with iodine or with oxygen.

Diphenyl Ether of Benzopinacol. When a colorless solution of this compound in naphthalene is heated, a red color is produced; this color is attributed to the formation of diphenylphenoxymethyl radicals.



Free Alkyl, Aryl, and Other Simple Radicals

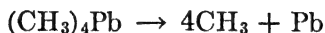
Free Alkyl Radicals. In 1929–1931 Paneth and co-workers⁷⁹ demonstrated the existence of free methyl and ethyl radicals. To prepare free

⁷⁷ Favorsky and Nazarov, *Bull. soc. chim.*, [5] **1**, 46 (1934).

⁷⁸ Gomberg and Bachmann, *J. Am. Chem. Soc.*, **49**, 236 (1927).

⁷⁹ Paneth and Hofeditz, *Ber.*, **62**, 1335 (1929); Paneth and Lautsch, *Ber.*, **64**, 2702 (1931); Paneth and Herzfeld, *Z. Elektrochem.*, **37**, 577 (1931).

methyl, vapors of tetramethyllead were carried by a rapid stream of hydrogen under reduced pressure (1–2 mm.) through a tube which was heated strongly (600–800°) at one point *A*. The tetramethyllead was decomposed by the heat as was evident from the deposition of a lead mirror at *A*; among the products of decomposition was gaseous methyl which may be supposed to originate from the reaction



The presence of free methyl was detected in various ways. A lead mirror was deposited at *B* farther along the tube and was allowed to cool to room temperature. Now, when decomposition of tetramethyllead was produced at *A*, the lead mirror at *B* gradually disappeared as it was removed by chemical combination with the methyl radicals to form tetramethyllead. If the mirror at *B* was more than a certain distance (32 cm. under the conditions employed) from the source *A* of the methyl radicals, the mirror was not removed, an indication that the free methyl radicals decomposed within a short time. From a measurement of the relative rates at which standard mirrors were removed at various distances from the source *A*, the "half-life" period of the methyl radical was calculated to be of the order of 0.006 second at a pressure of 2 mm. in hydrogen; this means that one-half of the total amount of free methyl radicals will be decomposed in that length of time.

The free ethyl radical has been prepared by thermal decomposition of tetraethyllead; its half-life is of the same order as that of free methyl. Evidence has been obtained of the formation of the free benzyl radical $\text{C}_6\text{H}_5\text{CH}_2$ (half-life about 0.006 second), but the higher alkyl radicals such as *n*-propyl and *n*-butyl appeared to be unstable at the high temperatures and decomposed immediately into unsaturated compounds and smaller free radicals or hydrogen atoms.



The free *n*-propyl and isopropyl radicals have been produced, however, by photochemical decomposition of di-*n*-propyl ketone and diisopropyl ketone respectively.¹⁰⁶ Each was found to have a half-life of about 0.004 second under the conditions employed.

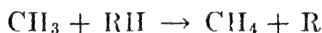
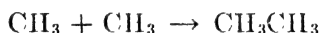
Free methyl, and to a certain extent free ethyl, can be obtained conveniently by pyrolysis of hydrocarbons and other compounds.^{80, 81}

⁸⁰ Rice and Rice, "Aliphatic Free Radicals," The Johns Hopkins Press, Baltimore (1935).

⁸¹ Rice, Johnston, and Evering, *J. Am. Chem. Soc.*, **54**, 3529 (1932); Rice and Herzfeld *ibid.*, **56**, 284 (1934).

When vapors of hexane at 1-3 mm. pressure are passed through a tube which is heated at one portion to about 800°, the hydrocarbon disintegrates and gives methyl radicals and a smaller proportion of ethyl radicals. Free methyl and ethyl radicals have also been prepared by interaction of sodium vapor and alkyl iodide in gaseous form at low pressures, $\text{C}_2\text{H}_5\text{I} + \text{Na} \rightarrow \text{C}_2\text{H}_5 + \text{NaI}$.⁸²

The chief reaction of methyl and of ethyl radicals at low pressure and room temperature in the absence of other reagents is recombination on the walls to give ethane and *n*-butane respectively; at higher temperatures the ethyl radical also disproportionates to give ethylene and ethane. Both methyl and ethyl readily abstract a hydrogen atom from saturated molecules to give methane and ethane respectively.



The alkyl radicals combine with iodine to form alkyl iodides and react with a number of other elements, usually in the form of mirrors, to form alkyl derivatives. Thus, by combination with free methyl radicals zinc is converted to dimethylzinc $(\text{CH}_3)_2\text{Zn}$, antimony to trimethylstibine $(\text{CH}_3)_3\text{Sb}$ and tetramethyldistibyl $(\text{CH}_3)_2\text{SbSb}(\text{CH}_3)_2$, arsenic to trimethylarsine $(\text{CH}_3)_3\text{As}$ and diacodyl $(\text{CH}_3)_2\text{AsAs}(\text{CH}_3)_2$, mercury to dimethylmercury $(\text{CH}_3)_2\text{Hg}$, and bismuth to the trimethyl derivative.

Free Aryl Radicals. Evidence has been obtained of the transitory existence of the free phenyl radical in the gaseous state and in solution. It appears to be formed in the reaction between sodium vapor and bromobenzene at high temperature and at low pressure⁸³ and in the thermal decomposition of tetraphenyllead; in these reactions the chief reaction of the phenyl radical is dimerization to biphenyl.

Hey and Waters⁸⁴ have summarized the reactions of the phenyl radical in solution. According to them the short-lived phenyl radical shows no tendency to dimerize to biphenyl in solution. Instead it reacts with practically any molecule with which it comes in contact. It abstracts a hydrogen atom from a non-aromatic solvent to form benzene and takes up a chlorine atom from a non-aromatic halide to give chlorobenzene.

⁸² Hartel and Polanyi, *Z. physik. Chem.*, **B11**, 97 (1930); Hartel, Meer, and Polanyi, *ibid.*, **B19**, 139 (1932); Wieland, "Die Hydrazine," Enke, Stuttgart (1913), pp. 187, 189

⁸³ Horn and Polanyi, *Z. physik. Chem.*, **B25**, 151 (1934); Allen and Brown, *Trans Faraday Soc.*, **34**, 463 (1938).

⁸⁴ Hey and Waters, *Chem. Rev.*, **21**, 169 (1937).

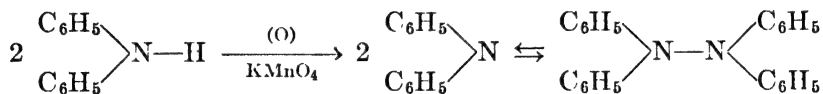
With neutral aromatic liquids it reacts to give *o*- and *p*-derivatives of biphenyl; the phenyl group enters *ortho* and *para* to the substituent even when the substituent is the nitro group.

Other Simple Free Radicals. Nef⁵ sought to prove that certain classes of organic compounds such as the isonitriles contain bivalent carbon and that numerous types of reactions take place through the intermediate formation of substituted methylene radicals, as for example CH_3CH . His attempts to prepare the free methylene radical CH_2 were unsuccessful; reactions designed to give this radical yielded ethylene instead. Now, it appears that the methylene radical is capable of existence. It is formed along with nitrogen by pyrolysis of diazomethane ($350\text{--}600^\circ$), $\text{CH}_2\text{N}_2 \rightarrow \text{CH}_2 + \text{N}_2$. The methylene radical removes mirrors of tellurium, antimony, and arsenic, but unlike the alkyl radicals it does not combine with zinc or lead.⁸⁵

The CN radical is formed by interaction of sodium and BrCN and other cyanogen halides in a highly diluted gas reaction⁸² and by thermal dissociation of cyanogen NC-CN at 1200° .⁸⁶ Spectroscopic evidence has been obtained of the existence of OH, NH, CH, CS, and similar radicals as well as charged radicals of the type CH^+ and CH_2^+ . These radicals have been observed in thermal decompositions or in the electric discharge in gases but they have lives so short that a study of their chemical properties is exceedingly difficult or impossible.⁸⁷

OTHER TYPES OF FREE RADICALS

Diarylamino Radicals. The tetraarylhydrazines were discovered by Wieland⁸⁸ in 1911. They are obtained as colorless solids by careful oxidation of diarylamines; thus, diphenylamine gives tetraphenylhydrazine when oxidized by potassium permanganate in cold acetone solution.



The intermediate diphenylamino radicals associate practically completely in solution at room temperature. When, however, a colorless solution of tetraphenylhydrazine in toluene is heated above 70° the greenish brown color of the diphenylamino radicals appears; when the

⁸⁵ Rice and Glasebrook, *J. Am. Chem. Soc.*, **55**, 4329 (1933); **56**, 2381 (1934).

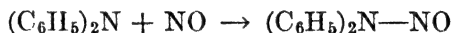
⁸⁶ Kistiakowsky and Gershinowitz, *J. Chem. Phys.*, **1**, 432 (1933).

⁸⁷ "Free Radicals," *Trans. Faraday Soc.*, **30**, 1-248 (1934), a report on a symposium on free radicals.

⁸⁸ Wieland, "Die Hydrazine," Enke, Stuttgart (1913); Wieland and Lecher, *Ann.* **381**, 206 (1911); Wieland, *Ber.*, **48**, 1078 (1915).

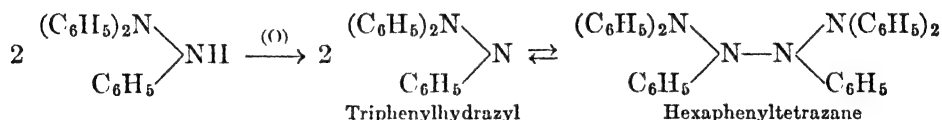
solution is cooled the color disappears. In general, groups such as NO_2 and C_6H_5 on the benzene nuclei tend to depress dissociation of the tetraarylhydrazines, and groups such as CH_3 , OCH_3 , and $(\text{CH}_3)_2\text{N}$ increase dissociation. Only one compound dissociated sufficiently to allow measurements to be made. Tetra-(*p*-dimethylaminophenyl)-hydrazine was found to be dissociated to the extent of 10 per cent in a dilute benzene solution and 20 per cent in a dilute nitrobenzene solution.

Unlike triarylmethyls, the diarylamino radicals do not react with oxygen or with iodine. The reaction most frequently employed for characterizing these radicals is the absorption of nitric oxide. If nitric oxide is passed into a solution of tetraphenylhydrazine at 90° , a quantitative yield of *N*-nitrosodiphenylamine is obtained.



From a study of the kinetics of the nitric oxide reaction it was found that the half-life of tetraphenylhydrazine is about 3 minutes at 100° and the energy of activation for the dissociation process is about 30 kcal.⁸⁹ The free diarylamino radicals combine with triphenylmethyl to form compounds of the type $\text{R}_2\text{N}-\text{C}(\text{C}_6\text{H}_5)_3$ and with sodium to give the sodium derivative of the diarylamine, $\text{R}_2\text{N}-\text{Na}$. Solutions of the tetraarylhydrazines are unstable, for the diarylamino radicals readily undergo disproportionation; thus, diphenylamino radicals give diphenylamine and *N,N'*-diphenyldihydrophenazine.

Triarylhydrazyls. By dehydrogenation of triarylhydrazines, R_2NNHR , by mild oxidizing agents as lead peroxide, Goldschmidt⁹⁰ obtained a class of compounds known as hexaaryltetrazanes. The triarylhydrazyl radicals are formed as intermediates, and these associate to the hexaaryltetrazane.



The compounds are extremely unstable, spontaneous decomposition occurring even at low temperatures (-80°). Like the diarylamino radicals, the triarylhydrazyls combine with nitric oxide and with triphenylmethyl. Measurements of the paramagnetism of α,α -diphenyl- β -2,4,6-trinitrophenylhydrazyl indicate that this radical does not associate to the tetrazane even in the solid state.⁹

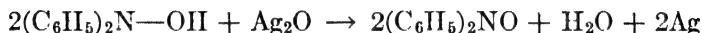
Much more stable radicals of this type are obtained by introducing an acyl group in place of one aryl group; the radicals diarylacetylhy-

⁸⁹ Cain and Wiselogle, *J. Am. Chem. Soc.*, **62**, 1163 (1940).

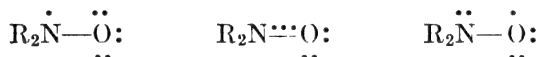
⁹⁰ Goldschmidt, *Ber.*, **53**, 44 (1920); Goldschmidt and Bader, *Ann.*, **473**, 137 (1929).

drazyl, $R_2NNCOCH_3$, and diarylbenzoylhydrazyl, $R_2NNCOC_6H_5$, are examples of this type of radical. The radical α,α -di-*p*-anisyl- β -benzoylhydrazyl ($p\text{-CH}_3\text{OC}_6\text{H}_4$)₂N—NCOC₆H₅ does not associate in acetone even at -50° . In contrast to the rapid dissociation of hexaarylethanes, the dissociation of the substituted tetrazanes is exceedingly slow.

Diarylnitrogen Oxides. Oxidation of N-diphenylhydroxylamine in ether solution at 0° by silver oxide yields diphenylnitrogen oxide, which can be isolated in the form of dark red crystals.⁹¹



The free radical nature of the diarylnitrogen oxides has been confirmed by paramagnetic susceptibility measurements. Of the following three electronic structures which may be written for these free radicals, Pauling²⁴ prefers the structure containing the three-electron bond but considers it probable that there is some resonance involving the other structures.

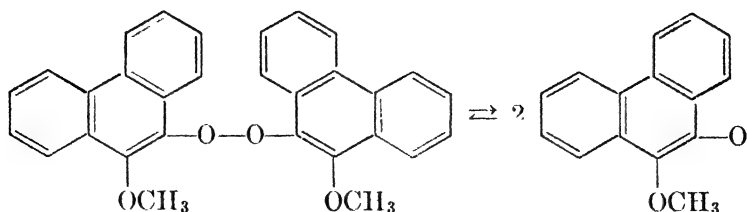


In general, the diarylnitrogen oxides are unstable compounds which decompose in a few hours. Introduction of nitro groups into the benzene nuclei stabilizes the molecule to such an extent that the free radical can be kept unchanged for several months. The diarylnitrogen oxides combine readily with nitric oxide and other odd molecules. The primary product of the reaction between diphenylnitrogen oxide and nitric oxide appears to be the N-nitroso derivative $(\text{C}_6\text{H}_5)_2\text{NO}(\text{NO})$ which then undergoes rearrangement to the more stable molecule, phenyl-*p*-nitrophenylamine. Triphenylmethyl instantly decolorizes a red solution of diphenylnitrogen oxide; here, too, the primary addition product $(\text{C}_6\text{H}_5)_2\text{N—O—C}(\text{C}_6\text{H}_5)_3$ undergoes further reaction to products which are unknown. With hydrogen iodide, iodine is liberated as the oxide is reduced to the diarylamine.

Aroxy Radicals. By mild oxidation of certain phenols there are produced diarylperoxides R—O—O—R , which are capable of dissociating into aroxy radicals $\text{R—O}\cdot$.⁹² The most stable products are obtained from 9-methoxy-, 9-ethoxy-, and 9-chloro-10-phenanthrol. Thus oxidation of 9-methoxy-10-phenanthrol in ether solution by lead peroxide gives the 9-methoxy-10-phenanthroxy radical which associates reversibly to bis(9-methoxy-10-phenanthryl)-peroxide.

⁹¹ Wieland and Offenbacher, *Ber.*, **47**, 2113 (1914); Wieland and Roth, *Ber.*, **53**, 210 (1920); Wieland and Kögl, *Ber.*, **55**, 1798 (1922); Cambi, *Gazz. chim. ital.*, **63**, 579 (1933).

⁹² Pummerer and co-workers, *Ber.*, **47**, 1472, 2957 (1914); **52**, 1416 (1919); Goldschmidt and Schmidt, *Ber.*, **55**, 3197 (1922).



The peroxide is colorless, but the free radicals are greenish yellow in solution. This particular radical is formed to the extent of 37 per cent in a dilute solution and the corresponding 9-ethoxy-10-phenanthroxy radical 62 per cent under the same conditions.

Like the tetraaryldibenzoyltetrazanes the diarylperoxides dissociate very slowly into the aroxy radicals and equilibrium is reached only after several hours. As a result the concentration of aroxy radicals in the equilibrium mixture can be determined by titration with hydrazobenzene solution, which reacts with the radical only.



The aroxy radicals are not readily affected by atmospheric oxygen, and they do not react with iodine or with nitric oxide. They combine with triphenylmethyl to give the triphenylmethyl ether of the phenol $\text{R}-\text{O}-\text{C}(\text{C}_6\text{H}_5)_3$ and with potassium to form the salt ROK , and are reduced to the phenol by zinc and acetic acid, by hydrogen iodide, and by phenylhydrazine.

Arylthiyl Radicals. Analogous to the diarylperoxides are the diaryl-disulfides $\text{RS}-\text{SR}$, which appear to dissociate into the free arylthiyl radicals RS .⁹³ Diphenyldisulfide, which is a colorless solid, gives a yellow



solution whose color deepens when the temperature is raised. Under mild conditions the phenylthiyl radical $\text{C}_6\text{H}_5\text{S}$ reacts with triphenylmethyl, with metallic sodium, and with metallic silver and forms $\text{C}_6\text{H}_5\text{SC}(\text{C}_6\text{H}_5)_3$, $\text{C}_6\text{H}_5\text{SNa}$, and $\text{C}_6\text{H}_5\text{SAg}$ respectively.

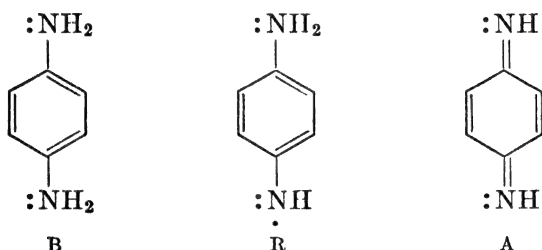
Semiquinone Radicals. Michaelis and his collaborators⁹⁴ have studied an interesting class of free radicals known as semiquinones. These radicals correspond to the intermediate stage between two members of a system capable of being converted readily into each other by a bivalent oxidation or reduction (involving the removal or addition of two electrons respectively). For example, deeply colored semiquinone radicals are

⁹³ Schönberg, *Trans. Faraday Soc.*, **30**, 17 (1934).

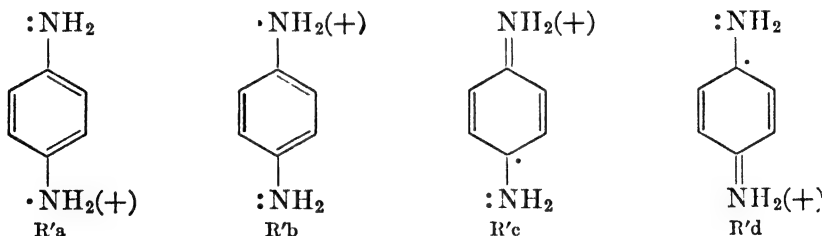
⁹⁴ Michaelis, *Chem. Rev.*, **16**, 243 (1935); Michaelis *et al.*, *J. Am. Chem. Soc.*, **60**, 202, 214, 1667, 1678 (1938).

formed as intermediates in the reduction of suitable quinones to hydroquinones and in the oxidation of aromatic diamines to the diimines. In these systems an equilibrium is established between two moles of the free radical (R) and its disproportionation products, oxidized form (A) and reduced form (B), $2R \rightleftharpoons A + B$. The existence of the semiquinone radicals has been established by potentiometric methods, by magnetometric measurements, and by colorimetric means.

A typical example of semiquinone formation is the production of a so-called Wurster dye by oxidation of *p*-phenylenediamine (or the *N*-alkyl derivative of the diamine) in acid solution. In neutral solution the three components of the system may be represented as follows:



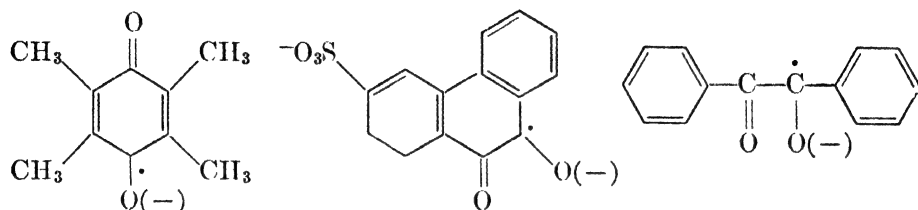
In neutral solution it is not possible to detect the intermediate radical (R), but in moderately acid solution a stable form (R') is formed by addition of a proton. As a result of the increased possibilities for resonance involving such forms as R'a, R'b, R'c, R'd, and the like, the radical becomes stabilized. Indeed, the free radicals of this type with the amino groups completely methylated are even more stable than the corresponding diimines.



Similarly constructed semiquinone radicals are formed by reduction of phenazines, flavin dyestuffs (including vitamin B₂), indophenols, indamines, and thiazines.

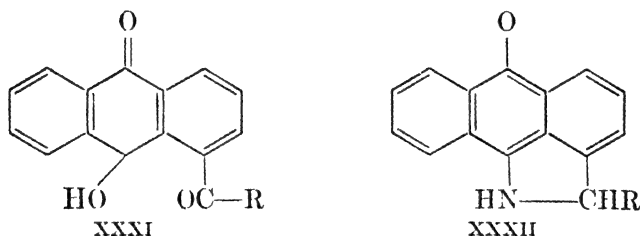
Stable semiquinones are obtained from suitable quinones and 1,2-diketones when the reduction is carried out in alkaline solution. Resonance among equivalent structures is possible in the anion, but this condition is destroyed when a hydrogen atom is present on one of the

oxygen atoms, which occurs in acid or neutral solutions. Semiquinone radicals have been obtained in alkaline solution from duroquinone, 3-phenanthrenequinonesulfonic acid, and benzil. In the following formulas only one of the forms contributing to the resultant resonance state is shown.



The last-mentioned semiquinone radical gives rise to the purple color which is observed when sodium hydroxide is added to an alcoholic solution of benzil $\text{C}_6\text{H}_5\text{COCOC}_6\text{H}_5$ and benzoin $\text{C}_6\text{H}_5\text{COCH}(\text{OH})\text{C}_6\text{H}_5$. The purple radical is also produced as an intermediate during the oxidation of benzoin in alkaline solution. In the dilute solutions in which these radicals are studied the free radical has little tendency to dimerize.

Examples of neutral semiquinone radicals are the hydroxyanthronyls (XXXI), which are formed by addition of a single atom of hydrogen to a molecule of the quinone, and the arylpyrrolinoanthroxy radicals (XXXII) of Scholl,⁹⁵ to which the following structures have been assigned:



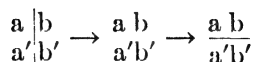
APPLICATION OF THE CONCEPT OF FREE RADICALS

In 1858 Kekulé⁹⁶ expressed his views on the manner in which reactions take place. He objected to the customary method of formulating reactions involving double decompositions as $\text{aa}' + \text{bb}' \rightarrow \text{ab} + \text{a'b}'$ because the formulation gave no indication of what went on during the reaction and was likely to lead to the erroneous conclusion that radicals exist in the free state during the exchange. According to him the

⁹⁵ Scholl, *Ber.*, **54**, 2376 (1921); Scholl, Dehnert, and Semp, *Ber.*, **56**, 1633 (1923); Scholl and Böttger, *Ber.*, **64**, 1878 (1931).

⁹⁶ Kekulé, *Ann.*, **106**, 129 (1858).

simplest expression of the reaction involved the formation of an intermediate addition complex, and he wrote the reaction in the following manner:

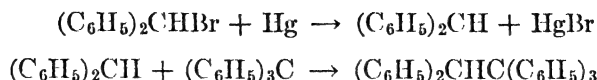


It is true that in certain reactions intermediate addition complexes are formed. On the other hand, there is abundant evidence that many reactions proceed through the intermediate formation of fragments, either ions or free radicals. The ionic mechanism has been particularly successful in interpreting reactions which proceed most readily in aqueous solution or in an ionizing solvent and reactions which are promoted by a polar environment, and those, such as hydrolysis, which are catalyzed by ions. Free radicals play an important role in many photochemical and thermal decompositions, and in reactions which occur in liquids of low dielectric constant and in gases.

The literature abounds in discussions of reactions in which the intermediate formation of free radicals is postulated. Often no definite proof could be obtained that the radicals were actually formed, but the results were most readily explained on the basis of radicals. This is especially true of reactions carried on in the liquid phase or in solution. In the gas reactions the short-lived radicals such as methyl, ethyl, and phenyl can often be detected by the Paneth effect on mirrors, and their formation can be deduced from the isolation of the dimers formed by association of the free radicals. In solution these extremely reactive radicals have little chance to dimerize, for they attack practically any molecule with which they collide. As a result, products are encountered which result from the action of the radicals on the solvent. Stable radicals such as the triarylmethyls can usually be detected without difficulty. In the discussion which follows, examples of reactions have been chosen in which more or less definite proof has been obtained that free radicals are involved.

Wurtz-Fittig and Allied Reactions. Hexaarylethanes and other compounds capable of dissociating into free radicals are generally obtained through association of free radicals initially formed in the reaction. By analogy with the formation of hexaarylethanes one can reasonably assume that the formation of *sym.*-tetraphenylethane from diphenylbromomethane and a metal proceeds through the intermediate formation and association of diphenylmethyl radicals. Support for this view was obtained when the reaction was carried out in the presence of triphenylmethyl.⁵⁷ If equivalent amounts of triphenylmethyl and diphenylbromomethane in benzene are shaken with mercury, the principal product

(90 per cent) is pentaphenylethane and the reaction may be formulated as follows:

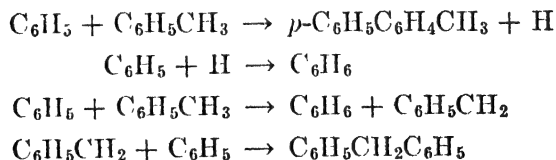


The diphenylmethyl radicals are "captured" by the triphenylmethyl radicals as soon as they are formed and do not associate to the tetraphenylethane.

In a similar manner, the diarylmethyl radicals formed by interaction of the halide and a metal have been found to react with oxygen more rapidly than association takes place. When diphenylchloromethane reacts with silver a quantitative yield of *sym*-tetraphenylethane is obtained, but when the reaction is carried out in the presence of oxygen only a few per cent of *sym*-tetraphenylethane are produced; the chief products are benzophenone, benzohydrol, and diphenylmethyl ether, formed by oxidation of the intermediate diphenylmethyl radicals. Similar results have been obtained with a number of diarylmethylchlorides.⁹⁷

There has been a great deal of discussion whether free radicals are formed as intermediates in the Wurtz-Fittig reaction (p. 539). Without doubt, in many reactions organosodium derivatives are formed as intermediates, but this does not exclude the intermediate formation of free radicals as well. It will be recalled that the free ethyl radical was obtained by interaction of sodium and ethyl iodide in the gas phase.

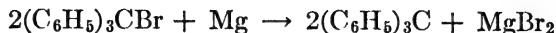
A free radical mechanism was proposed to account for the products of the reaction between sodium and chlorobenzene, namely, benzene, biphenyl, 4-phenylbiphenyl, 2-phenylbiphenyl, 2,2'-diphenylbiphenyl, and triphenylene.⁹⁸ The formation of these compounds can be understood if one assumes the intermediate formation of the phenyl radical, which can associate, disproportionate to benzene and phenylene radicals (which can add phenyl radicals to give the phenylbiphenyls), and react with some of the substances present. When the reaction was carried out in toluene, biphenyl formation was completely suppressed and a large quantity (nearly 50 per cent) of benzene was produced in addition to 4-methylbiphenyl and diphenylmethane. These products may result from intermediate organosodium compounds or from reactions such as



⁹⁷ Wuis and Mulder, *Rec. trav. chim.*, **57**, 1385 (1938); Nauta and Mulder, *ibid.*, **53** 1062 (1939).

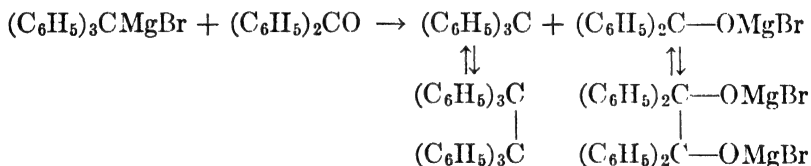
⁹⁸ Bachmann and Clarke, *J. Am. Chem. Soc.*, **49**, 2089 (1927).

Grignard Reaction (p. 495). It has been definitely proved that the preparation of the Grignard reagent triphenylmethylmagnesium bromide proceeds through the intermediate formation of the free radical triphenylmethyl.⁹⁹

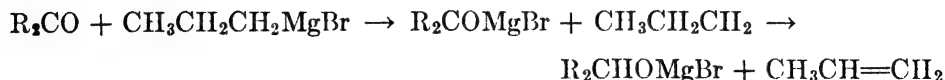


When one-half of the total amount of magnesium has reacted, the solution contains triphenylmethyl (and hexaphenylethane) but no Grignard reagent. Similarly, triphenylmethyl is an intermediate in the preparation of triphenylmethylsodium from triphenylchloromethane and sodium. As soon as all the chloride has reacted, the yellow solution containing triphenylmethyl rapidly becomes intensely red as triphenylmethylsodium is formed.¹⁰⁰ It has been suggested that other Grignard reagents are formed through a free-radical mechanism.

Further evidence of the formation of free radicals as intermediates has been obtained from a study of the reactions of Grignard reagents. Triphenylmethylmagnesium bromide reacts with benzophenone to form the two radicals triphenylmethyl and bromomagnesium-benzophenone-ketyl; the two radicals then associate to the corresponding symmetrical compounds.



This type of reaction is not uncommon. The chief products of the reaction between benzylmagnesium chloride and methyl iodide are bibenzyl and ethane. The reaction between benzophenone and *n*-propylmagnesium bromide (and other Grignard reagents) (p. 646) which gives benzohydrol as the principal product in addition to propylene has been explained on the basis of radicals.¹⁰¹



It is difficult to account for the formation of ethane and ethylene in addition to *n*-butane in the reaction between ethylmagnesium bromide and ethyl bromide unless free ethyl radicals are assumed to be produced

⁹⁹ Gomberg and Bachmann, *ibid.*, **52**, 2455 (1930).

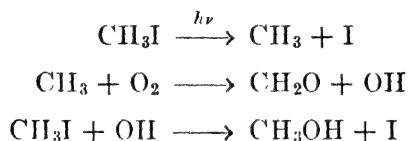
¹⁰⁰ Schlenk and Ochs, *Ber.*, **49**, 609 (1916).

¹⁰¹ Blicke and Powers, *J. Am. Chem. Soc.*, **51**, 3378 (1929).

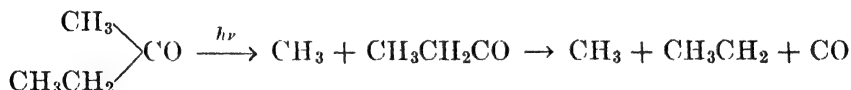
as intermediates. Then the process becomes clear, for the ethyl radicals may disproportionate as well as associate.

Photochemical Reactions. Dissociation of triarylmethyl bromides into the triarylmethyl radicals takes place when their solutions are irradiated or subjected to the action of cathode rays. If a solution of triphenylbromomethane in benzene is exposed to sunlight or light in the near ultra-violet region, a deep yellow color develops. In contact with air or oxygen the irradiated solution deposits crystals of triphenylmethylperoxide.¹⁰²

A considerable number of simple free radicals have been observed in the photolysis of organic compounds. Not only free alkyl and acyl radicals but also radicals of the type OH, O₂H, CCl₃, COCl, CH, NH, NH₂, and many others are now used freely to explain the results of photochemical reactions. The results obtained by irradiation of alkyl iodides in the presence of oxygen, which leads to the formation of alcohols and aldehydes, have been explained on the basis of an initial dissociation of the alkyl iodide into the alkyl radical and atomic iodine.¹⁰³



The photochemical decomposition of aldehydes and ketones has received considerable attention. The production of free methyl and ethyl radicals appears to be achieved by irradiation of ketones by light of certain wave length (2900 Å). Methyl ethyl ketone decomposes into methyl and propionyl radicals and the latter then break down into ethyl radicals and carbon monoxide.¹⁰⁴



The free alkyl radicals then combine to form ethane, propane, and *n*-butane. In a similar manner, photochemical decomposition of acetone at room temperature yields the free methyl and acetyl radicals which can associate to form ethane and diacetyl. Above 60° no diacetyl is formed because of the decomposition of the acetyl radical to methyl and carbon monoxide.¹⁰⁵ The acetyl radical has a life even shorter than that of the alkyl radicals.

¹⁰² Halford and Anderson, *Proc. Natl. Acad. Sci. U. S.*, **19**, 759 (1933).

¹⁰³ Bates and Spence, *J. Am. Chem. Soc.*, **53**, 1689 (1931)

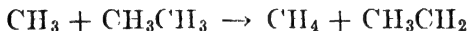
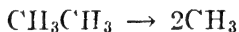
¹⁰⁴ Norrish, Ref. 87, p. 107.

¹⁰⁵ Glazebrook and Pearson, *J. Chem. Soc.*, 567 (1937).

On exposure to light, di-*n*-propyl ketone yields free *n*-propyl radicals. Diisopropyl ketone gives isopropyl radicals initially, but these subsequently isomerize to *n*-propyl radicals, for the product of the reaction between the radicals and mercury was di-*n*-propylmercury.¹⁰⁶ Photolysis of acetaldehyde gives the methyl radical and the unstable CHIO radical as primary products, which then undergo further reaction (see thermal decomposition), and irradiation of ketene $\text{CH}_2=\text{CO}$ yields the methylene radical and carbon monoxide.

The photochemical production of phosgene from carbon monoxide and chlorine takes place through the following steps involving a chain reaction carried on by chlorine atoms and the COCl radical: $\text{Cl}_2 \rightarrow 2\text{Cl}$; $\text{Cl} + \text{CO} \rightarrow \text{COCl}$; $\text{COCl} + \text{Cl}_2 \rightarrow \text{COCl}_2 + \text{Cl}$.¹⁰⁷ Kharasch and Brown¹⁰⁸ have found that irradiation of a mixture of oxalyl chloride, or phosgene, and cyclohexane gives a good yield of cyclohexanecarboxylic acid chloride. They believe that the COCl radical, formed by photolysis of the acid chlorides, is probably an important intermediate in the reaction. Similarly, the photochemical sulfonation of aliphatic acids and saturated hydrocarbons with sulfuryl chloride has been explained by a free-radical mechanism.¹⁰⁹ In the latter reaction the following formulation has been suggested: $\text{SO}_2\text{Cl}_2 \rightarrow \text{SO}_2 + \text{Cl}_2$; $\text{Cl}_2 \rightarrow 2\text{Cl}$; $\text{Cl} + \text{RH} \rightarrow \text{R} + \text{HCl}$; $\text{R} + \text{SO}_2 \rightarrow \text{RSO}_2$; $\text{RSO}_2 + \text{Cl}_2 \rightarrow \text{RSO}_2\text{Cl} + \text{Cl}$.

Thermal Decompositions. It has been shown that many types of aliphatic compounds, hydrocarbons, ethers, aldehydes, and ketones, when heated in the range 700–1100° C., decompose into free radicals which can be detected by the Paneth effect on mirrors.⁸¹ In the pyrolysis of hydrocarbons Rice has been able to predict semi-quantitatively the products of such decompositions on the basis of free-radical formation. In these reactions, chain reactions are initiated by the alkyl radicals initially produced. Thermal decomposition of ethane has been formulated in the following manner:



¹⁰⁶ Glazebrook and Pearson, *ibid.*, 1777 (1936). But see also Kharasch, Kane, and Brown, *J. Am. Chem. Soc.*, **63**, 526 (1941).

¹⁰⁷ Bodenstein, *Z. physik. Chem.*, **130**, 422 (1927); Bodenstein and Onoda, *ibid.*, **131**, 153 (1928).

¹⁰⁸ Kharasch and Brown, *J. Am. Chem. Soc.*, **62**, 454 (1940).

¹⁰⁹ Kharasch and Read, *ibid.*, **61**, 3089 (1939); Kharasch and Brown, *ibid.*, **62**, 925 (1940); Kharasch, Chao, and Brown, *ibid.*, **62**, 2393 (1940).

The chain is terminated by collision of the ethyl groups with hydrogen atoms; the length of the chain is about 100 cycles.

Thermal decomposition of acetaldehyde gives methane, carbon monoxide, and small amounts of hydrogen. The reaction appears to take place through a chain reaction initiated by free radicals, and the following mechanism is one that has been proposed: $\text{CH}_3\text{CHO} \rightarrow \text{CH}_3 + \text{CO} + \text{H}$; $\text{H} + \text{CH}_3\text{CHO} \rightarrow \text{H}_2 + \text{CH}_3\text{CO} (\rightarrow \text{CH}_3 + \text{CO})$; $\text{CH}_3 + \text{CH}_3\text{CHO} \rightarrow \text{CH}_4 + \text{CO} + \text{CH}_3$. Decomposition of the acetaldehyde can be carried out at a temperature at which the pure aldehyde is inert by addition of some azomethane, $\text{CH}_3\text{N}=\text{NCH}_3$. The azomethane on pyrolysis yields free methyl radicals¹¹⁰ which initiate the chain reaction involved in the decomposition of the aldehyde.¹¹¹ This same technique has been applied to the photochemical decomposition of acetaldehyde¹¹² at room temperature and to the thermal decomposition of hydrocarbons.

Triarylmethyl radicals are produced not only by thermal dissociation of hexaarylethanes but also by thermolysis of a number of other types of compounds. Azotriphenylmethane, $(\text{C}_6\text{H}_5)_3\text{CN}=\text{NC}(\text{C}_6\text{H}_5)_3$, decomposes into triphenylmethyl and nitrogen even at 0° , and ditriphenylmethyldisulfide $(\text{C}_6\text{H}_5)_3\text{CS}-\text{SC}(\text{C}_6\text{H}_5)_3$ and certain other sulfur compounds yield triphenylmethyl on decomposition. The thermal decomposition of benzeneazotriphenylmethane, $(\text{C}_6\text{H}_5)_3\text{CN}=\text{NC}_6\text{H}_5$, has been the subject of considerable investigation. Gomberg⁶ found that very little tetraphenylmethane is produced on decomposition of the compound. From the results of the investigations of Wieland and his collaborators¹¹³ it is reasonable to assume that the primary reaction is decomposition into triphenylmethyl, nitrogen, and phenyl, $(\text{C}_6\text{H}_5)_3\text{CN}=\text{NC}_6\text{H}_5 \rightarrow (\text{C}_6\text{H}_5)_3\text{C} + \text{N}_2 + \text{C}_6\text{H}_5$. There is no difficulty in detecting the triphenylmethyl radicals, but the short-lived phenyl radicals are more elusive. The phenyl radical does not dimerize to form biphenyl but reacts rapidly with the solvent employed. Thus, it abstracts a hydrogen atom from hydrocarbons like hexane to form benzene; it removes a chlorine atom from carbon tetrachloride to form chlorobenzene; it reacts with benzene to give biphenyl, with toluene to form 2- and 4-methylbiphenyl, and with chlorobenzene to give 4-chlorobiphenyl.¹¹⁴ Similar products have been obtained in other reactions in which free phenyl radicals appear to be formed.

Oxidation and Reduction Reactions. According to Ziegler²⁶ the first step in the reaction between triphenylmethyl and oxygen is the

¹¹⁰ Leermakers, *ibid.*, **55**, 3499 (1933).

¹¹¹ Allen and Sickman, *ibid.*, **56**, 2031 (1934).

¹¹² Blacet and Taurog, *ibid.*, **61**, 3024 (1939).

¹¹³ Wieland, *Ann.*, **514**, 145 (1934).

¹¹⁴ Hey, *J. Chem. Soc.*, 1966 (1934).

formation of very reactive radicals of the type $R_3C-O-O-$. These radicals then combine with triphenylmethyl radicals to give the peroxide. The free peroxide radical also reacts with undissociated hexaphenylethane: $R_3CO_2 + R_3CCR_3 \rightarrow R_3COOCR_3 + R_3C$. The radical liberated in this reaction takes up another molecule of oxygen, and the chain is continued. By adding an equivalent amount of pyrogallol, the chain reaction is inhibited (by reaction of the R_3COO radicals with pyrogallol) and a mole of oxygen is absorbed for *each* mole of triphenylmethyl radical.

Triphenylmethyl is found to be a catalyst for the oxidation of a number of compounds in virtue of the formation of the active peroxide radicals, which promote chain reactions, often of great length. Thus, chains of 55,000 units have been observed in the oxidation of dimethylbenzofulvene in the presence of a small amount of triphenylmethyl. The reaction is $R_3C + O_2 \rightarrow R_3CO_2$; $R_3CO_2 + A \rightarrow R_3C + AO_2$; $R_3C + O_2 \rightarrow R_3CO_2$; etc. The chain is broken when the peroxide radical combines with a triphenylmethyl radical to give triphenylmethylperoxide.

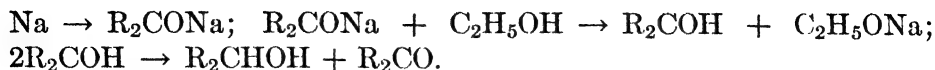
According to Michaelis,⁹⁴ bivalent oxidations (and reductions) proceed in steps involving the intermediate formation of free radicals, and he has actually demonstrated the existence of the free radicals (semiquinones) in all the familiar reversible oxidation-reduction systems. If A represents the reduced form, R the radical, and B the oxidized form, then the reaction proceeds in the steps, $A \rightleftharpoons R + e$; $R \rightleftharpoons B + e$.

The free radical C_6H_5NH appears to be formed as an intermediate in the oxidation of aniline by lead dioxide, for when the reaction is carried out in the presence of triphenylmethyl, N-triphenylmethylaniline $C_6H_5NHC(C_6H_5)_3$ is formed.¹¹⁵ Although spectroscopic evidence has been obtained of the presence of free CH_3 , CH_2 , and CH radicals in the inner cones of hydrocarbon flames where there is a limited supply of oxygen, it has not yet been decided definitely what part free radicals play in combustion.

Conant and Bigelow³⁶ have shown that in the reduction of malachite green and related compounds by soluble reducing agents free radicals are produced initially; these then react further with the reducing agent to give the leuco base. In the reduction of aromatic ketones to the hydrols by sodium amalgam and alcohol, the first step is the addition of sodium to the ketone to give a ketyl radical; the ketyl radical reacts with the alcohol to give equivalent amounts of hydrol and ketone, and the regenerated ketone then goes through a similar series of changes,¹¹⁶ $R_2CO +$

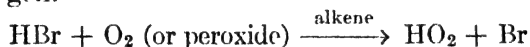
¹¹⁵ Goldschmidt and Wurzschnitt, *Ber.*, **55**, 3216 (1922).

¹¹⁶ Bachmann, *J. Am. Chem. Soc.*, **55**, 770 (1933).



Other Reactions. Hey and Waters⁸⁴ believe that free phenyl radicals are responsible for the products obtained in the Gomberg-Bachmann reaction.¹¹⁷ In this reaction biaryls are formed by addition of alkali to a mixture of a diazonium salt and an aromatic hydrocarbon or derivative, $\text{C}_6\text{H}_5\text{N}_2\text{Cl} + \text{C}_6\text{H}_6 + \text{NaOH} \rightarrow \text{C}_6\text{H}_5\text{C}_6\text{H}_5 + \text{N}_2 + \text{NaCl} + \text{H}_2\text{O}$. A highly reactive diazo hydroxide (or anhydride) formed by the action of the alkali on the diazonium salt is extracted by the aromatic liquid, and the reaction takes place in the organic solution. The phenyl radical initially produced reacts with benzene to form biphenyl and with some of the biphenyl to give 4-phenylbiphenyl; it reacts with toluene to give 2- and 4-methylbiphenyl, and with bromobenzene to give 2- and 4-bromobiphenyl.¹¹⁸ Nitrobenzene and cyanobenzene are attacked in the *para* position to give 4-nitrobiphenyl and 4-cyanobiphenyl respectively, contrary to the usual *meta* substitution of these compounds which takes place in ionic reactions. It appears that the abnormal substitution with these compounds serves as a test for the formation of phenyl radicals. Similar results have been obtained in the reaction between nitrosoacyl-arylamines and aromatic liquids.¹¹⁹

A free radical mechanism has been proposed to account for the abnormal addition of HBr to unsaturated compounds in the presence of peroxides or oxygen.¹²⁰



The addition of halogens to double and triple bonds in the presence of light may involve the intermediate formation of free radicals. Thus, the photochemical addition of bromine to acetylene involves the following chain reaction: $\text{Br}_2 \rightarrow 2\text{Br}$; $\text{HC}\equiv\text{CH} + \text{Br} \rightarrow \text{HC}=\dot{\text{C}}\text{HBr}$; $\text{HC}=\text{CHBr} + \text{Br}_2 \rightarrow \text{BrCH}=\text{CHBr} + \text{Br}$, and the addition of chlorine to *cis* and *trans* dichloroethylene follows a similar course.¹²¹ Transitory free radicals with free bonds on the terminal atoms have been postulated in polymerization processes.¹²²

¹¹⁷ Gomberg and Bachmann, *ibid.*, **46**, 2339 (1924).

¹¹⁸ Gomberg and Pernert, *ibid.*, **48**, 1372 (1926).

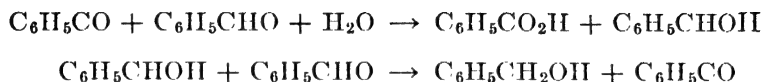
¹¹⁹ Grieve and Hey, *J. Chem. Soc.*, 1797 (1934).

¹²⁰ Kharasch, Engelmann, and Mayo, *J. Org. Chem.*, **2**, 288 (1937); Mayo and Walling, *Chem. Rev.*, **27**, 351 (1940).

¹²¹ Müller and Schumacher, *Z. physik. Chem.*, **B39**, 352 (1938).

¹²² Chalmers, *J. Am. Chem. Soc.*, **56**, 912 (1934); Staudinger and Lautenschläger, *Ann.*, **488**, 1 (1931).

Haber and Willstätter¹²³ see the work of free radicals in the Cannizzaro reaction and in many reduction (p. 643) and dehydrogenation reactions. A chain reaction is induced by a free radical which is formed initially from the substrate by removal of a hydrogen atom. In the Cannizzaro reaction it is assumed that the C_6H_5CO radical is produced through reaction of a molecule of benzaldehyde with the ion of a heavy metal present in minute amounts. The radical then initiates the following series of reactions:



There is a close parallelism between the addition reactions of the double bond in unsaturated compounds and those of the triply linked carbon atom in free radicals, and a number of investigators have been forced to the conclusion that the double linkage may open to a slight extent to a single bond with the formation of a biradical. Enzymes, according to Freundlich, may perhaps be free radicals which are stabilized because they are adsorbed at a suitable interface, and the function of certain enzymes in reactions is to produce a free radical from the substrate by removing a hydrogen atom. It has been suggested that the formation, addition, disproportionation, and polymerization of free radicals may play an important role in the process of biological synthesis and degradation of living cells, under the influence of mild reagents and low temperatures.

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¹²³ Haber and Willstätter, *Ber.*, **64**, 2844 (1931).

CHAPTER 7

UNSATURATION AND CONJUGATION

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INTRODUCTION

The ability to undergo addition reactions is the organic chemist's primary criterion of unsaturation, and the three distinct types of organic compounds which meet this requirement constitute the great bulk of organic chemistry. In substances of the first type, unsaturation is associated with a strained ring structure (p. 100) and addition reactions result in ring opening. Cyclopropane and ethylene oxide are examples. In substances of the second type, unsaturation is confined to a single atom, and addition reactions result in an increase in valence of that atom. Triphenylmethyl and trimethylamine are examples. In substances of the third type unsaturation is shared by two adjacent atoms. Ethylene and acetone are examples. This last type of unsaturated compound is by far the most common of the three, and it is the only type which will be dealt with in this chapter.

The six unsaturated groups will be considered: $C=C$, $C=O$, $C\equiv C$, $C=N$, $C\equiv N$, and NO_2 .* Frequently organic compounds contain more than one of these six unsaturated groups and in such cases the groups present may be alike or different. When more than one unsaturated group is present in a molecule the organic chemist distinguishes between three possibilities: twinned double bonds or systems, such as $C=C=C$, where two unsaturations are shared by the same atom; conjugated multiple linkages or systems, such as $C=C-C=O$, where alternate single and multiple linkages are present; and separated multiple linkages or systems, such as $C=C-(CH_2)_n-C=C$, where one or more saturated atoms separate the multiple linkages. Not all these possibilities can or need be considered in this chapter. The discussion will be confined to systems containing but one unsaturated group or one unsaturated group and an aromatic ring system, to twinned double bonds, and to conjugated systems.

Although unsaturation means primarily the ability to undergo addition reactions, there is also associated with it the activating effect which unsaturated groups exert on nearby atoms. Victor Meyer as early as 1872 observed the surprising reactivity of the α -hydrogen atoms in the nitroparaffins and later began a systematic search for other such activating or "negative" groups.¹ Later Henrich showed that all such activating groups were unsaturated.² The activating effects of unsatu-

* The nitroso ($N=O$) and azo ($N=N$) groups are not considered in this chapter. They are discussed in Sidgwick, "The Organic Chemistry of Nitrogen," new edition revised by Taylor and Baker, Clarendon Press, Oxford (1937), Chapter VII and pp. 431-437. The unsaturation present in nitrones, azoxy compounds, and amine oxides is covered in an article by Smith, *Chem. Rev.*, **23**, 193 (1938).

¹ Meyer and Stüber, *Ber.*, **5**, 399 (1872).

² Henrich, *Ber.*, **32**, 668 (1899).

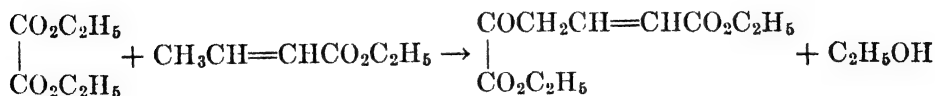
rated groups play a role in chemical reactivity exceeded in importance only by the addition reactions of these unsaturated groups. As the chemical behavior of the various unsaturated groups is described, the ways in which and the extent to which they activate adjacent atoms will be indicated.

Unsaturation of the type which is being discussed is almost universally represented at present by the double or triple bond with the understanding that each individual linkage represents a pair of shared electrons. This was not always the case. The ethylenic double bond, for example, was originally represented by a single linkage between two carbon atoms each of which possessed one free valence. It was soon recognized, however, that these free valences always occurred in pairs shared by two adjacent atoms and that addition reactions always saturated both free valences. From this point it was but a short step to represent the two free valences as combining with each other to form a second linkage between the two atoms involved. It was carefully stated that the double bond did not imply twice the strength of the single bond; rather, it implied reactivity by addition. It is important to realize that the current method of representing unsaturation by double or triple bonds reveals nothing about the rates at which addition reactions take place, nothing about the mode of addition where more than one mode is possible, and nothing about the mechanism of addition. Attempts to devise a representation of unsaturation which will convey this information have not so far been successful.

SYSTEMS CONTAINING ONE UNSATURATED GROUP OR ONE UNSATURATED GROUP AND AN AROMATIC RING

The Carbon-Carbon Double Bond

The carbon-carbon double bond, which is the most important example of unsaturation shared by two like atoms, gives rise to a wide variety of addition reactions and also serves to transmit the activating or inactivating effects of substituents or other unsaturated groups.³



Activation of adjacent atoms by the isolated ethylenic linkage is neither frequent nor striking. Probably the most important exceptions to this statement are the greater reactivity of the allyl halides as

³ Fuson, *Chem. Rev.*, **16**, 1 (1935); Blatt, *J. Org. Chem.*, **1**, 154 (1936).

compared with the propyl halides and the case of oxidation of the system $-\text{CH}=\text{CH}-\text{CH}_2-$ to furnish an α,β -unsaturated ketone.⁴

Reduction. Of the many addition reactions of the ethylenic linkage none is more general than the addition of hydrogen which, because of its wide applicability, is used to determine the number of ethylenic double bonds present in organic compounds. For the isolated ethylenic double bond, catalytic hydrogenation is the method *par excellence*; metal combinations are without effect.*

Catalytic hydrogenation may be carried out at the ordinary temperature and pressure when specially prepared, highly active forms of platinum and palladium are employed. Less expensive but also less effective is finely divided nickel whose use generally requires both high pressure and temperature or a vapor phase reduction. Improvements in the preparation of nickel catalysts⁵ have led to highly active material which will bring about the hydrogenation of many ethylenic compounds in the cold.⁶ Catalytic hydrogen adds most rapidly to isolated double bonds, less so to open-chain conjugated double bonds, and least of all to the conjugated double bonds present in aromatic ring systems. Consequently, by a suitable choice of catalyst, temperature, and pressure, hydrogenation may often be made selective⁷ and may almost always be made complete. The failure to reduce certain biphenyl derivatives is apparently the one case in which catalytic reduction of ethylenic linkages has not been possible.⁸

Oxidation. Under the general topic of oxidation a closely related group of reactions will be considered, some of which lead to the addition of an atom of oxygen or two hydroxyl groups to an ethylenic linkage, while the others lead to cleavage of the molecule at the double bond. The first few reactions are useful primarily in synthetic work; the remaining reactions are useful chiefly in degradative studies. Peracetic, perbenzoic, and monoperphthalic acids form epoxides by addition of an atom of oxygen to ethylenic linkages. The reaction is of somewhat

⁴ Semmler and Jakubowicz, *Ber.*, **47**, 1143 (1914); Blumann and Zeitschel, *Ber.*, **47**, 2623 (1914); Windaus, *Ber.*, **53**, 488 (1920).

* Metal combinations, which are discussed more fully in connection with the reduction of carbonyl compounds, will reduce the ethylenic side chain in styrene and its analogs but will not reduce the side chain in allylbenzene and its analogs. Toward metal combinations and toward a variety of other reagents, styrene and the substituted vinylbenzenes behave like substances containing a conjugated system of ethylenic double bonds. Consequently, those reactions of styrene and its analogs which are the reactions of conjugated systems will be discussed under that heading.

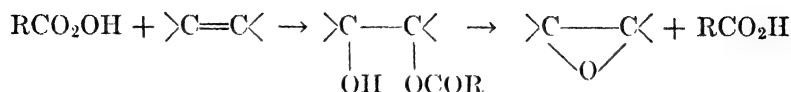
⁵ Covert and Adkins, *J. Am. Chem. Soc.*, **54**, 4116 (1932).

⁶ Dupont, *Bull. soc. chim.*, [5] **3**, 1021 (1936).

⁷ Späth, *Ber.*, **70A**, 83 (1937); Adkins, *Ind. Eng. Chem.*, **32**, 1189 (1940). Compare reference 50(b), and p. 797.

⁸ Waldeland, Zartman, and Adkins, *J. Am. Chem. Soc.*, **55**, 4234 (1933).

limited applicability, and epoxides are not the sole products. According to Böseken, who has made the most thorough study of the reaction, the process involves the addition of a mole of peracid followed by the elimination of a mole of acid.⁹



Many ethylenic compounds on treatment with the iodo-silver benzoate complex furnish the benzoates of 1,2-glycols.¹⁰ In a few cases the acetates of 1,2-glycols can be obtained by treatment of an ethylenic compound with lead tetraacetate.¹¹ The 1,2-glycols themselves result from the catalyzed addition of hydrogen peroxide to ethylenic double bonds.¹²

Potassium permanganate reacts with many but not all ethylenic double bonds. A safe generalization is that permanganate will react readily with any ethylenic linkage where each ethylenic carbon atom holds at least one atom of hydrogen, and it will react with many ethylenic linkages where one ethylenic carbon atom holds at least one atom of hydrogen, but it will rarely react with completely substituted ethylenic linkages. Obviously, Baeyer's qualitative test for the ethylenic linkage using permanganate is not reliable. However, when it does react, permanganate is extremely useful. It can be used in alkaline, neutral, or acidic solution and in water or acetone. If it is used in cold, buffered, dilute, aqueous solution the reaction leads to the addition of two hydroxyl groups and the product is a 1,2-glycol.¹³ Ordinarily, however, the oxidation is carried further and the molecule is cleaved between the carbon atoms originally joined by the double bond to furnish aldehydes, ketones, and acids. Such oxidative cleavage with permanganate is often used in the determination of structure. In so doing it should be kept in mind that ethylenic linkages frequently shift in the presence of alkali so that the end products of permanganate oxidation, though showing accurately enough the whole of the parent molecule, may not indicate the original position of an ethylenic linkage.

⁹ Böseken and Elsen, *Rec. trav. chim.*, **48**, 363 (1929); Böseken and Schneider, *J. prakt. Chem.*, **131**, 285 (1931); Böhme, *Ber.*, **70**, 379 (1937).

¹⁰ Prévost, *Compt. rend.*, **196**, 1129 (1933); *Atti X° congr. intern. chim.*, **3**, 318 (1939) [*C. A.*, **33**, 8187³ (1939)].

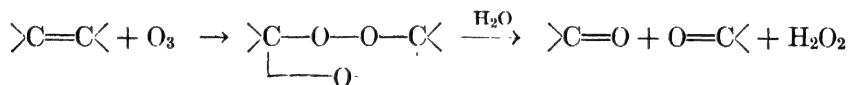
¹¹ Dimroth and Schweizer, *Ber.*, **56**, 1375 (1923); Criegee, *Ann.*, **481**, 263 (1930).

¹² Milas and Sussman, *J. Am. Chem. Soc.*, **59**, 2345 (1937); Milas, Sussman, and Mason, *ibid.*, **61**, 1844 (1939). Compare Treibs, *Ber.*, **72**, 5 (1939). With certain ethylenes the glycols formed are cleaved to aldehydes by the same reagent. Criegee and Richter, *Ann.*, **522**, 94 (1936).

¹³ Wagner, *Ber.*, **21**, 1230, 3347 (1888).

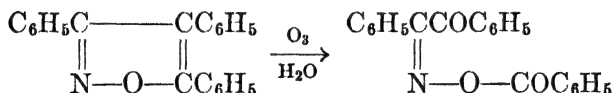
Chromic acid functions as an effective complement to permanganate as a reagent for the oxidative cleavage of ethylenic double bonds. Simple ethylenic compounds, which are oxidized satisfactorily by permanganate, are attacked too vigorously by chromic acid for it to be of value. Highly substituted ethylenic compounds, particularly highly phenylated compounds, which are unaffected by permanganate are frequently oxidized by chromic acid to furnish significant products.

The addition of ozone to the ethylenic double bond followed by decomposition of the resulting ozonides—ozonolysis—is the most general and reliable procedure for oxidative cleavage with simultaneous location of the double bond,¹⁴ although ozone is not so specific a reagent for the ethylenic linkage as was formerly believed.¹⁵ The method has the decided advantage that it permits isolation of the primary cleavage products, for the excess oxidant, ozone, can be removed before the ozonide is cleaved. In oxidations, with permanganate and chromic acid the cleavage products are exposed to the action of the oxidant.



Care must be taken in decomposing ozonides not only because they are often highly explosive but also because the hydrogen peroxide formed in this process may destroy the primary cleavage products. This latter complication may be largely offset by reductive decomposition,¹⁶ but the decomposition of ozonides is more complex than the simple formulation given above.¹⁷

Ozone reacts more rapidly with open-chain ethylenic linkages than with those present in aromatic ring systems, and it reacts more rapidly with a carbon-carbon than with a carbon-nitrogen double bond. Thus the ethylenic linkages in the side chain are attacked on ozonization of phenylated ethylenes, and the ozonization of triphenylisoxazole furnishes the benzoate of benzil monoxime.¹⁸



¹⁴ Long, *Chem. Rev.*, **27**, 437 (1940).

¹⁵ Durland and Adkins, *J. Am. Chem. Soc.*, **61**, 429 (1939).

¹⁶ Fischer, Düll, and Ertel, *Ber.*, **65**, 1467 (1932); Whitmore and Church, *J. Am. Chem. Soc.*, **54**, 3710 (1932); Church, Whitmore, and McGrew, *ibid.*, **56**, 176 (1934).

¹⁷ Briner, Perrottet, Paillard, and Susz, *Helv. Chim. Acta*, **19**, 1163 (1936); Briner and de Nemitz, *ibid.*, **21**, 748 (1938); Briner, de Nemitz, and Perrottet, *ibid.*, **21**, 762 (1938); Briner, Franck, and Perrottet, *ibid.*, **22**, 224 (1939). These articles contain a discussion of the structure of ozonides.

¹⁸ Meisenheimer, *Ber.*, **54**, 3206 (1921).

In general, however, the presence of a carbon-nitrogen double bond leads to complications which may render the results of ozonolysis inconclusive. Quantitative data on the rates of ozone addition to ethylenic compounds indicate that the loading of ethylenic carbon atoms with phenyl groups or halogen atoms decreases the rate of addition.¹⁹

Ethylenic hydrocarbons may be converted to ethylene oxides by means of oxygen and a catalyst, usually silver, at high temperatures.²⁰

Halogens. Chlorine, bromine, and iodine add to many ethylenic compounds. Of the three halogens, bromine is the most useful; chlorine is too reactive, and its use is often accompanied by substitution, while iodine adds to but few ethylenic compounds. With simple ethylenic compounds, the reaction with chlorine at elevated temperatures and in the presence of small amounts of oxygen results almost completely in substitution. Thus, propylene furnishes allyl chloride.²¹

The instant decoloration of a bromine solution without the evolution of hydrogen bromide is a valuable qualitative test for an ethylenic linkage, but a negative result with this test is not conclusive. As an approximation, the rule which was given for the oxidation of ethylenic compounds with permanganate may be applied to the addition of bromine: bromine will add to any ethylenic linkage where each ethylenic carbon atom holds at least one atom of hydrogen, and it will add to many ethylenic linkages where one of the ethylenic carbon atoms holds at least one atom of hydrogen, but it will rarely add to completely substituted ethylenic linkages. This rule is a very gross approximation because it does not take into account the chemical nature of the substituents. Unfortunately not a great deal of precise information is available about the effects of single substituents on the addition of bromine, but it has long been known that the loading of an ethylenic linkage with halogen atoms or aromatic groups will hinder addition or prevent it completely.²²

Frequently the products of addition of the halogens to ethylenic linkages will dissociate under suitable conditions to regenerate the ethylenic compound and halogen—in other words, the process is reversible. In the great majority of reactions, however, addition is either essentially complete or else it does not take place to an appreciable extent so that the primary concern is with rates of reaction. In this connection it should be emphasized that bromine addition is very

¹⁹ Noller, Carson, Martin, and Hawkins, *J. Am. Chem. Soc.*, **58**, 24 (1936).

²⁰ Carbide and Carbon Chemicals Corp., U. S. pat. 2,156,341 [*C. A.*, **33**, 5869 (1939)].

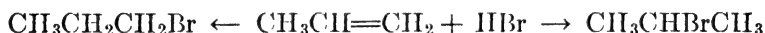
²¹ Groll, Hearne, Rust, and Vaughan, *Ind. Eng. Chem.*, **31**, 1239 (1939); Vaughan and Rust, *J. Org. Chem.*, **5**, 449 (1940); Rust and Vaughan, *ibid.*, **5**, 472 (1940).

²² Bauer, *Ber.*, **37**, 3317 (1904); **40**, 918 (1907); Reich, van Wijek, and Waelle, *Helv Chim. Acta*, **4**, 242 (1921); Ingold and Ingold, *J. Chem. Soc.*, 2354 (1931).

sensitive to catalysis both by polar molecules and by light. The mechanism of halogen additions has been extensively investigated. These additions are, in almost every instance, *trans*, and the two atoms of halogen add stepwise, not simultaneously. In polar solvents the second step frequently involves some addend other than a second halogen atom so that along with 1,2-dihalogen addition products other substances are formed.²³

Not only the halogens but also thiocyanogen²⁴ and iodine monochloride and monobromide will add to ethylenic compounds. The addition of iodine monochloride and monobromide to the unsaturated glycerides present in such industrially important oils as cottonseed, olive, and the like, can be made a quantitative process by operating under strictly controlled conditions. The "iodine numbers" thus obtained, which are a measure of the unsaturated constituents present, serve as a basis for the control of quality of the oils.²⁵ The addition of the iodine monohalides is not satisfactory, however, as a general analytical method for ethylenic compounds.²⁶

Halogen Acids. Hydrogen fluoride,²⁷ chloride, bromide, and iodide add to ethylenic compounds. The addition is often reversible, and the rate of addition, which is usually slow, is markedly subject, save with the fluoride, to catalytic acceleration. The halogen acids furnish the first important examples of unsymmetrical addends, and when hydrogen bromide, for example, adds to an unsymmetrically substituted ethylenic linkage two isomeric products may result.



These possibilities were recognized early in the development of organic chemistry, and Markownikoff²⁸ in 1870 presented a generalization, based on observations of the behavior of a number of relatively simple ethylenic compounds, which has made it possible to predict in many reactions the major product of halogen acid addition. This generalization, known as Markownikoff's rule, may be stated as follows: when a halogen acid (HX) adds to an unsymmetrical ethylenic compound,

²³ A review of the evidence for stepwise addition of halogen and a discussion of its stereochemical implications will be found in Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York (1940), pp. 147-151. Examples of halogen addition involving the solvent are reported by Weber, Hennen, and Vogt, *J. Am. Chem. Soc.*, **61**, 1457 (1939).

²⁴ Söderbäck, *Ann.*, **443**, 142 (1925); Kaufmann and Oehring, *Ber.*, **59**, 187 (1926).

²⁵ Wijs, *Ber.*, **31**, 750 (1898). Details of the method can be found in most books dealing with commercial analytical methods.

²⁶ Faragher, Gruse, and Garner, *Ind. Eng. Chem.*, **13**, 1044 (1921).

²⁷ Grosse and Linn, *J. Org. Chem.*, **3**, 26 (1938).

²⁸ Markownikoff, *Ann.*, **153**, 256 (1870).

the halogen (X) usually appears on the carbon atom carrying the smaller number of hydrogen atoms or the larger number of alkyl groups. This rule is approximate, not exact. The greater the differences in the chemical nature of the substituents on the ethylenic carbon atoms, the more closely it is obeyed. Generally, however, it does serve to predict the major product of the reaction. While Markownikoff's rule predicts adequately the mode of addition of hydrogen fluoride, chloride, and iodide, hydrogen bromide often adds in the opposite sense—abnormal addition.²⁹ Recently it has been found that the addition of hydrogen bromide to simple ethylenic compounds follows Markownikoff's rule in the absence of peroxides and that in the presence of peroxides or ferromagnetic metals abnormal addition occurs.³⁰ Proper allowances for the peroxide effect and for solvent effects³¹ are clarifying many of the discrepancies in the literature dealing with the addition of hydrogen bromide to ethylenic compounds.* It must be emphasized, however, that this discussion of Markownikoff's rule has dealt only with its accuracy. No generally accepted theoretical explanation of the course of additions to simple ethylenic compounds has been advanced.³²

Inorganic Oxygen Acids. The inorganic oxygen acids, sulfuric and nitric, add to ethylenic double bonds.† Sulfuric acid of various concentrations up to 100 per cent either adds to ethylenic linkages as H and OSO₃H in accordance with Markownikoff's rule to furnish alkyl sulfuric acids, or serves to add a molecule of water at the ethylenic linkage and form alcohols. It has generally been assumed that the alcohol synthesis proceeds *via* an alkyl sulfuric acid which undergoes subsequent hydrolysis. However, this interpretation is inconsistent with the facts that the yields of alcohols are favored by the use of dilute acid and low temperatures and that alcohols can be isolated from the reaction mixtures under conditions such that the alkyl sulfuric acids are not appreciably hydrolyzed.³³

²⁹ Kharasch, Kleiger, and Mayo, *J. Org. Chem.*, **4**, 428 (1939).

³⁰ Kharasch and Mayo, *J. Am. Chem. Soc.*, **55**, 2468 (1933), and later articles. For a summary of work on the peroxide effect in the addition of halogen acids and other addends to ethylenic compounds, see Mayo and Walling, *Chem. Rev.*, **27**, 351 (1940).

³¹ Sherrill, Mayer, and Walter, *J. Am. Chem. Soc.*, **56**, 926 (1934); Sherrill, *ibid.*, **56**, 1645 (1934); Linstead and Rydon, *J. Chem. Soc.*, 2002 (1934); Kharasch and Potts, *J. Am. Chem. Soc.*, **58**, 57 (1936); Michael and Wiener, *J. Org. Chem.*, **4**, 531 (1939); O'Connor, Baldinger, Vogt, and Hennion, *J. Am. Chem. Soc.*, **61**, 1454 (1939).

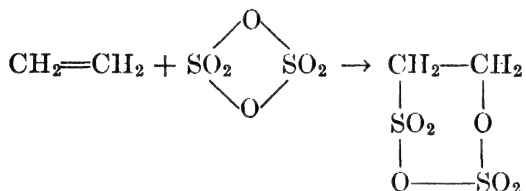
* The peroxide effect plays a part in the reactions between ethylenes and other addends than hydrogen bromide. See below under Miscellaneous, p. 641.

³² Michael, *J. Org. Chem.*, **4**, 519 (1939); Michael and Wiener, *ibid.*, **4**, 531; **5**, 389 (1940).

† Many ethylenic compounds rearrange and polymerize or polymerize directly in the presence of mineral acids. Compare p. 641.

³³ Brooks and Humphrey, *J. Am. Chem. Soc.*, **40**, 822 (1918); Plant and Sidgwick, *J. Soc. Chem. Ind.*, **40**, 14T (1921).

In the absence of water it has been believed, following Wieland,³⁴ that sulfuric and nitric acids added as $\text{HO}-\text{SO}_3\text{H}$ and $\text{HO}-\text{NO}_2$ with subsequent esterification of the hydroxyl group in the compounds thus formed. In support of this view was the isolation of ethionic acid, carbyl sulfate, and β -nitroethyl nitrate from the interaction of ethylene with sulfuric and with nitric acids. Michael has challenged this interpretation and has shown that the formation of ethionic acid and carbyl sulfate takes place only when fuming sulfuric acid is used.³⁵ For their formation he suggested the following processes:



Using nitric acid and ethylene Michael found that addition takes place as $\text{H}-\text{ONO}_2$; the nitro esters and nitroalkylenes isolated by earlier investigators are the result of an indirect nitration by means of the nitrous oxides generated by oxidative side reactions (p. 176).³⁶

Hypohalogen Acids. Hypochlorous and hypobromous acids react readily with many ethylenic compounds. In certain of these reactions water solutions of the halogen are effective. When an alcohol is used as a solvent the product is often that substance which would be obtained by the addition of the alkyl hypohalite corresponding to the alcohol; compare the mechanism of halogen addition, p. 637. In hypohalite additions to unsymmetrical ethylenes both possible products are usually obtained, but the principal product results from the addition of hydroxyl to the carbon atom holding the smaller number of hydrogen atoms (contrast the mode of addition of halogen acids described on p. 638). The addition of hypochlorous acid to propylene furnishes the same mixture of isomers in the same proportion that is obtained by the ring opening of propylene oxide by hydrochloric acid.³⁷ In line with this fact is the suggestion that hypochlorous acid and ethylenes react first to give ethylene oxides and hydrochloric acid; the oxides are then opened by the hydrochloric acid to form chlorohydrins.³⁸

³⁴ Wieland and Sakellarios, *Ber.*, **52**, 898 (1919); **53**, 201 (1920); Wieland and Rahn *Ber.*, **54**, 1770 (1921).

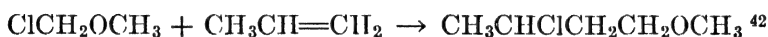
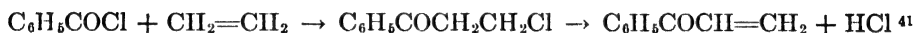
³⁵ Michael and Wiener, *J. Am. Chem. Soc.*, **58**, 294 (1936).

³⁶ Michael and Carlson, *ibid.*, **57**, 1268 (1935).

³⁷ Smith, *Z. physik. Chem.*, **93**, 59 (1919).

³⁸ Michael and Carlson, *J. Am. Chem. Soc.*, **57**, 1268 (1935).

Friedel-Crafts Reactions. A number of reactions may next be considered whereby paraffins, cycloparaffins, and aromatic hydrocarbons, phenols, acyl halides, and α -chloroethers may be added to ethylenic hydrocarbons. These reactions, which are brought about under the influence of catalysts such as the chlorides of aluminum, zinc, and bismuth, boron trifluoride, hydrogen fluoride, and sulfuric acid may be considered as variants of the Friedel-Crafts syntheses (pp. 179, 553).



They are applicable to a wide range of ethylenic compounds. Unless the reactions are carried out under carefully specified and controlled conditions complex mixtures of products are likely to result, for the same catalysts which are effective in the above addition processes are also the ones which usually polymerize ethylenic hydrocarbons.⁴³ Although these reactions are not of much importance in the laboratory, they are of tremendous importance in the manufacture of fuel for internal-combustion engines.

Miscellany. A final group of reactions, the addition of sulfur compounds, nitrogen compounds, and mercuric salts, remains to be considered. These addition reactions are of less general applicability than those already discussed, and their study has not progressed to the same extent as the study of the addition reactions considered earlier.

Sulfur chloride adds to many ethylenes: the reaction is the basis for the manufacture of mustard gas.



Sulfur and hydrogen sulfide react with ethylenes to form mercaptans so that the final products in the reaction between these substances and ethylenic hydrocarbons are the products resulting from the addition of

³⁹ Ipatieff, Grosse, Pines, and Komarewski, *ibid.*, **58**, 913 (1936); Ipatieff, Corson, and Pines, *ibid.*, **58**, 919 (1936).

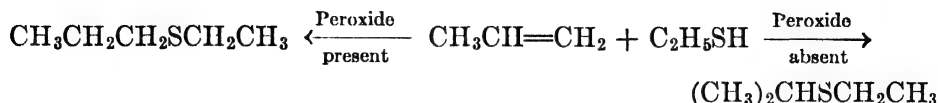
⁴⁰ Sowa, Hinton, and Nieuwland, *ibid.*, **54**, 3694 (1932); Niederl and Whitman, *ibid.*, **56**, 1966 (1934).

⁴¹ Norris and Couch, *ibid.*, **42**, 2329 (1920); Allen, Cressman, and Bell, *Can. J. Research*, **8**, 440 (1933); Colonge and Mostafavi, *Bull. soc. chim.*, [5] **6**, 335 (1939).

⁴² Scott, U. S. pat. 2,024,749 (1935); Straus and Thiel, *Ann.*, **525**, 151 (1936).

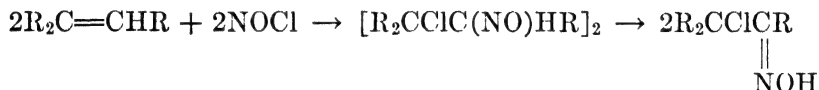
⁴³ Ipatieff and Grosse, *J. Am. Chem. Soc.*, **57**, 1616 (1935); **58**, 915 (1936); Nash and Mason, *Ind. Eng. Chem.*, **26**, 45 (1934).

mercaptans to the double bond.⁴⁴ The peroxide effect is encountered in the addition of mercaptans. In the addition of bisulfite to ethylenes

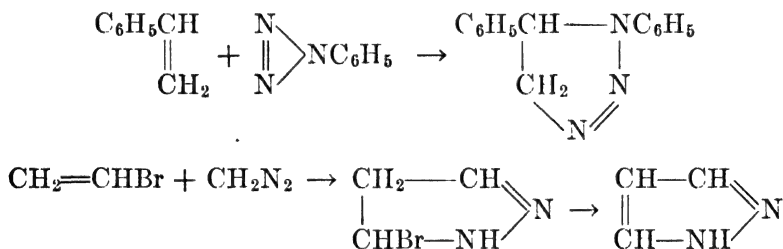


the presence of oxygen or peroxides is essential.⁴⁵

Nitrosyl chloride, nitrogen trioxide, and nitrogen tetroxide add to many trisubstituted ethylenes and have been widely used in the terpene series in order to secure solid derivatives. The bimolecular addition products originally formed undergo, whenever possible, a shift of a hydrogen atom to furnish oximes.⁴⁶



Recent studies on the trioxide and tetroxide additions indicate that the reactions are more complex than was formerly believed and that earlier generalizations are of doubtful validity.⁴⁷ Phenyl azide and diazomethane add to a limited number of ethylenes, the reactions serving as a method of synthesis of triazoles and pyrazoles.⁴⁸



Organomagnesium halides do not add to the ethylenic linkage. The elements of methoxymercuric acetate do add to ethylenes to give

⁴⁴ Posner, *Ber.*, **38**, 646 (1905); Ashworth and Burkhardt, *J. Chem. Soc.*, 1791 (1928); Carothers, *J. Am. Chem. Soc.*, **55**, 2008 (1933); Jones and Reid, *ibid.*, **60**, 2452 (1938); Ipatieff, Pines, and Friedman, *ibid.*, **60**, 2731 (1938); Mayo and Walling, *Chem. Rev.*, **27**, 351 (1940).

⁴⁵ Kharasch, May, and Mayo, *J. Org. Chem.*, **3**, 175 (1938); Kharasch, Schenck, and Mayo, *J. Am. Chem. Soc.*, **61**, 3092 (1939).

⁴⁶ Schmidt, *Ber.*, **35**, 2323, 3727 (1902); Schmidt and Leipprand, *Ber.*, **37**, 532 (1904); Wieland, *Ann.*, **424**, 71 (1921).

⁴⁷ Michael and Carlson, *J. Org. Chem.*, **4**, 169 (1939); **5**, 1, 14 (1940).

⁴⁸ Wolff, *Ann.*, **394**, 68 (1912); Alder and Stein, *Ann.*, **501**, 1 (1933); Oliveri-Mandalà *Gazz. chim. ital.*, **40** (1), 117 (1910); Wieland and Probst, *Ann.*, **530**, 274 (1937).

products stable in non-acidic media. The addition is accelerated by electron acceptors and retarded by electron donors.⁴⁹

The Carbon-Oxygen Double Bond

The carbonyl group occupies the same position of major importance among unsaturations shared by two unlike atoms which the ethylenic linkage holds among unsaturations shared by two like atoms, and the addition reactions of the carbonyl group are, for synthetic purposes at least, of greater importance than those of the ethylenic double bond. There are wide variations in the rates of addition to carbonyl compounds and equally wide variations in the positions of equilibrium of such of the addition reactions as are reversible. Detailed information on the relative reactivities of carbonyl compounds in addition reactions is found in Chapter 13 (p. 1049) and in the paragraphs below.

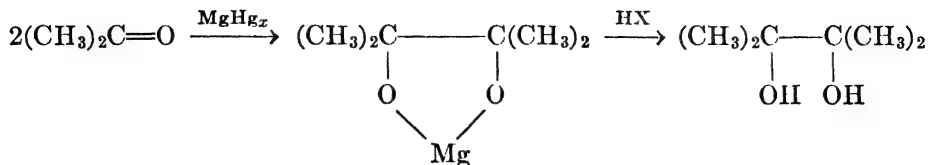
Reduction. In contrast with the ethylenic linkage which is amenable only to catalytic hydrogenation, the carbonyl group can be reduced both catalytically and by means of metal combinations. Catalytic reduction leads to the formation of primary alcohols from aldehydes and secondary alcohols from ketones. The carbonyl group often acts as a poison to platinum catalysts; the catalyst must then either be reactivated by frequent shaking with oxygen or protected by the addition of an iron salt. Such use of iron salts as promoters often makes possible the preferential reduction of a carbonyl group in the presence of an ethylenic linkage.⁵⁰

Metal combinations, which have not been considered up to this time, consist of a base metal (sodium, zinc, magnesium, and various amalgams) with a hydrogen donor which may be either an acid, a base, or a neutral molecule such as water or alcohol. Aldehydes on reduction with metal combinations furnish primary alcohols. Ketones, however, on similar treatment undergo bimolecular reduction and give almost exclusively 1,2-glycols, known as pinacols. When magnesium amalgam is used, a magnesium derivative which furnishes the pinacol on acidification can be isolated. This fact indicates the importance of the metal in bimolecular reductions, and it has been suggested that such reductions proceed through the addition of the active metal to the oxygen atom with formation of a complex having a free valence. This complex can combine either with a similar complex or with a second atom of metal. Decompo-

⁴⁹ Wright, *J. Am. Chem. Soc.*, **57**, 1993 (1935); Birks and Wright, *ibid.*, **62**, 2412 (1940).

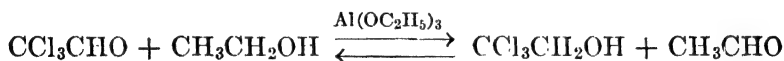
⁵⁰ (a) Adams and Garvey, *ibid.*, **48**, 477 (1926); (b) Weygand and Werner, *Ber.*, **71**, 2469 (1938); (c) Sauer and Adkins, *J. Am. Chem. Soc.*, **59**, 1 (1937).

sition of the resulting metallic derivatives by the hydrogen donor furnishes the final products.⁵¹



Complete reduction of the carbonyl group to a methylene group is also possible using metallic combinations (the Clemmensen procedure employing amalgamated zinc and hydrochloric acid⁵²) or by way of the hydrazones or semicarbazones and alkoxides (Wolff-Kishner method⁵³). In certain cases this type of reduction can be effected catalytically.⁵⁴

A third method for reducing many aldehydes and some ketones to the corresponding alcohols depends upon the simultaneous dehydrogenation of an alcohol to a carbonyl compound.⁵⁵



The reaction is reversible, and the carbonyl compound formed must be removed in order to carry the reaction to completion. As may be observed from the illustration, this process permits the reduction of carbonyl groups even when there are present other reactive groups which would be attacked by the ordinary reducing agents. Many reductions of carbonyl compounds which have been ascribed to the Grignard reagent are in reality due to the process just described. For example, the reduction of benzaldehyde on treatment with an insufficient amount of ethylmagnesium bromide is a result of the reaction between the bromomagnesium alkoxide of ethylphenylcarbinol and the excess benzaldehyde.⁵⁶ A limited number of carbonyl compounds can be reduced by the Grignard reagent itself; the process is entirely different from the alkoxide reduction and will be described in connection with the addition reactions of the Grignard reagent.

Organic acids are extremely difficult to reduce. This probably indi-

⁵¹ Willstätter, Seitz, and Bumm, *Ber.*, **61**, 871 (1928).

⁵² Clemmensen, *Ber.*, **46**, 1838 (1913); **47**, 51, 681 (1914); Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

⁵³ Wolff, *Ann.*, **394**, 86 (1912).

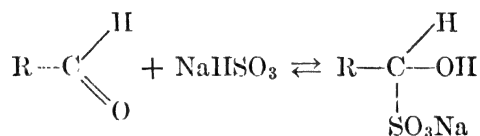
⁵⁴ Failliebin, *Compt. rend.*, **177**, 1118 (1923).

⁵⁵ Meerwein and Schmidt, *Ann.*, **444**, 221 (1925); Lund, *Ber.*, **70**, 1520 (1937); Bersin, *Z. angew. Chem.*, **53**, 266 (1940). For a special method of reducing aromatic aldehydes to primary alcohols with simultaneous oxidation of formaldehyde to formic acid see the Cannizzaro reaction (p. 649).

⁵⁶ Meisenheimer, *Ann.*, **446**, 76 (1926).

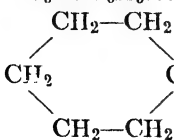
cates the absence of a true carbonyl group in the acids themselves, for, as soon as the dissociable hydrogen atom is removed by esterification or by the formation of derivatives such as lactams, anhydrides, or chlorides, reduction takes place more readily.

Alkali Bisulfite. On treatment with an aqueous solution of an alkali bisulfite, almost all aldehydes, many methyl ketones, and a few cyclic ketones will add a mole of bisulfite and form alkali salts of α -hydroxy-sulfonic acids.⁵⁷ These salts are crystalline solids, sparingly soluble in the presence of excess bisulfite, and are of practical importance in the isolation of carbonyl compounds. Since, further, the addition reaction is reversible, the alkali bisulfite can be destroyed either by alkali or acid and the carbonyl compounds can thus be regenerated; the addition products are useful in the purification of carbonyl compounds.



With simple carbonyl compounds the rate of bisulfite addition is decreased by increasing the size or the complexity of the hydrocarbon residues attached to the carbonyl carbon atom. The data in Table I

TABLE I⁵⁸

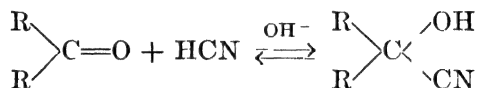
| Substance | Per Cent Reacted After One Hour | | |
|---|---------------------------------|--|---|
| | KHSO ₃ | NH ₂ OH | C ₆ H ₅ NHNH ₂ |
| Any aldehyde..... | 70-90 | (C ₆ H ₅ CHO 85) | .. |
| CH ₃ COCH ₃ | 22 | 82 | 66 |
| CH ₃ COCH ₂ CH ₃ | 14 | 75 | 52 |
| CH ₃ COCH ₂ CH ₂ CH ₃ | 12 | 72 | 38 |
| CH ₃ COCH(CH ₃) ₂ | 3 | 33 | 15 |
| C ₂ H ₅ COC ₂ H ₅ | 2 | 38 | 11 |
| CH ₃ COC ₆ H ₅ | 1 | 8 | 4 |
|  | 35 | 92 | 40 |

⁵⁷ Raschig and Prah!, *Ber.*, **61**, 179 (1938); Lauer and Langkammerer, *J. Am. Chem. Soc.*, **57**, 2360 (1935); Caughlan and Tartar, *ibid.*, **63**, 1265 (1941).

⁵⁸ Petrenko-Kritschenko and Kantscheff, *Ber.*, **39**, 1452 (1906). Compare also Stewart, *J. Chem. Soc.*, **87**, 186 (1905).

illustrating these effects are of fundamental importance in any consideration of the addition reactions of the carbonyl group, for, as will be seen later, toward other addends the order of reactivity of simple carbonyl compounds is, with few exceptions, the same as that toward bisulfite. This statement is not to be interpreted as indicating that the steric effects just mentioned are the only factors determining the rate of addition to the carbonyl group but rather that they are usually the predominant factors.

Hydrogen Cyanide. In the presence of a base, hydrogen cyanide will add reversibly to the carbonyl group to form an hydroxynitrile (p. 1035).⁵⁹ This reaction, which is of wider applicability than the bisulfite addition, is a valuable synthetic tool.



Grignard Reagent (p. 495). The Grignard reagent adds irreversibly to formaldehyde to yield primary alcohols; to other aldehydes and to esters of formic acid to furnish secondary alcohols; and to ketones and esters of organic acids other than formic to yield tertiary alcohols. Three other reactions, reduction, replacement of α -hydrogen, and condensation, may, however, interfere with the normal addition of the Grignard reagent to the carbonyl group. Thus, when diisopropyl ketone is treated with isopropylmagnesium bromide, the products are diisopropylcarbinol and propylene; when acetomesitylene is treated with methylmagnesium iodide it evolves one molar equivalent of methane and forms an iodomagnesium enolate from which acetomesitylene can be recovered on acidification; and when ethyl phenylacetate is treated with isopropylmagnesium bromide, condensation to α,γ -diphenylacetoacetic ester occurs. The correlation of these three reactions and addition with the structures of various carbonyl compounds and Grignard reagents is illustrated in Table II.

From the data in Table II it is seen that an increase in the size or the complexity of the groups present in the carbonyl compounds or the reagent generally decreases the extent of the normal addition reaction. However, size and complexity of the substituent groups are not the only significant factors. A definite amount of complexity causes less interference with addition when it is present in the ketone than when it is present in the reagent. These complications so curtail the effectiveness of the Grignard reagent as a synthetic tool that, by present methods,

⁵⁹ Lapworth, *J. Chem. Soc.*, **83**, 995 (1903); Lapworth and Manske, *ibid.*, 2533 (1928) 1976 (1930).

TABLE II ⁶⁰

| Substance | CH ₃ MgI | <i>n</i> -C ₄ H ₉ MgBr or <i>n</i> -C ₃ H ₇ MgBr | <i>iso</i> - C ₃ H ₇ MgBr | <i>tert.</i> - C ₄ H ₉ MgCl |
|---|---------------------|--|--|--|
| CH ₃ CHO..... | AA | | A | A |
| (CH ₃) ₂ CHCHO..... | A | | AA | AR |
| (CH ₃) ₃ CCHO..... | | AA | AR | RR |
| CH ₃ COCH ₃ | AA | AA | AA(C) | A |
| C ₂ H ₅ COC ₂ H ₅ | AA | AA | AA | C |
| CH ₃ COCH(CH ₃) ₂ | AA | | AA(R) | |
| CH ₃ COC(CH ₃) ₃ | AA | AR | EC | EC |
| (CH ₃) ₂ CHCOCH(CH ₃) ₂ | AA | AR | RR | RR |
| (CH ₃) ₃ CCOC(CH ₃) ₃ | AA+ | RR | RR | RR |
| (CH ₃) ₂ CHCO ₂ C ₂ H ₅ | | | RR | |
| C ₆ H ₅ CH ₂ CO ₂ C ₂ H ₅ | | | EE, CC | |
| C ₆ H ₅ COC ₆ H ₅ | AA | R | | AA |

A = addition. R = reduction. † = no reaction with C₆H₅MgBr. C = condensation. E = replacement of α -H. A single letter indicates approximately 50 per cent reaction; a double letter indicates greater than 50 per cent reaction.

it is not possible to prepare secondary alcohols containing two tertiary groups or tertiary alcohols containing more than two branched-chain groups. The mechanism of reduction by organomagnesium halides is not agreed upon; reduction can generally be avoided by using instead of a Grignard reagent the corresponding organolithium compound, and frequently the organolithium compounds will add to carbonyl groups that are unattacked by the Grignard reagent.⁶¹

Reformatsky Reaction (p. 548). The Reformatsky reaction⁶² is related to the Grignard reaction. The preparation of a Grignard reagent from a bromoester is not practicable, for the organomagnesium compound formed from one molecule reacts with the ester group present in a second molecule. Treatment of an ester of an α - or β -bromoacid with zinc in the presence of an aldehyde or ketone results in the formation of an ester of a β - or γ -hydroxyacid. The Reformatsky reaction, because of its selectivity and wide applicability, is a valuable method for the synthesis of hydroxyesters and their dehydration products.

All the addition reactions of the carbonyl group which have been considered up to this point can be formulated in the same way: the

⁶⁰ Conant and Blatt, *J. Am. Chem. Soc.*, **51**, 1227 (1929); Conant, Webb, and Mendum, *ibid.*, **51**, 1246 (1929); Blatt and Stone, *ibid.*, **54**, 1495 (1932); Kharasch and Weinhouse, *J. Org. Chem.*, **1**, 209 (1936).

⁶¹ Wittig and Petri, *Ber.*, **68**, 924 (1935).

⁶² Reformatsky, *Ber.*, **28**, 2842 (1895); Haberland and Heinrich, *Ber.*, **72**, 1222 (1939).

addition of hydrogen, or a metal which is replaced by hydrogen in the final product, and a second fragment A. The mode of addition is always such that hydrogen adds to oxygen while the balance of the addend goes to carbon, and the primary addition products always contain an hydroxyl group.

| CARBONYL COMPOUND | ADDEND | PRODUCT |
|--|--|--|
| $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C} \\ \diagdown \\ \text{O} \end{array}$ | $\text{H}-\text{A}$ | $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C}-\text{OH} \\ \diagdown \\ \text{A} \end{array}$ |
| $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C} \\ \diagdown \\ \text{O} \end{array}$ | $\text{H}-\text{H}$ | $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C}-\text{OH} \\ \diagdown \\ \text{H} \end{array}$ |
| $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C} \\ \diagdown \\ \text{O} \end{array}$ | $\text{H}-\text{SO}_3\text{Na}$ | $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C}-\text{OH} \\ \diagdown \\ \text{SO}_3\text{Na} \end{array}$ |
| $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C} \\ \diagdown \\ \text{O} \end{array}$ | $\text{H}-\text{CN}$ | $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C}-\text{OH} \\ \diagdown \\ \text{CN} \end{array}$ |
| $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C} \\ \diagdown \\ \text{O} \end{array}$ | $\text{XMg}-\text{R}$ | $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C}-\text{OMgX} \\ \diagdown \\ \text{R} \end{array} \rightarrow \begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C}-\text{OH} \\ \diagdown \\ \text{R} \end{array}$ |
| $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C} \\ \diagdown \\ \text{O} \end{array}$ | $\text{BrZn}-\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$ | $\begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C}-\text{OZnBr} \\ \diagdown \\ \text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 \end{array} \rightarrow \begin{array}{c} \text{H} \\ \diagup \\ \text{R}-\text{C}-\text{OH} \\ \diagdown \\ \text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 \end{array}$ |

In the mode of addition to the carbonyl group there is no such ambiguity as is observed in the addition of unsymmetrical reagents to the ethylenic double bond.

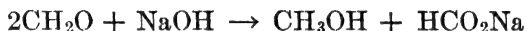
Synthesis and Condensation. The same formulation, addition as H and A, applies also to the reactions of condensation and synthesis with carbonyl compounds which are next to be considered. In these two groups of reactions, however, the primary hydroxyl-containing addition products are seldom isolated; instead the reactions usually go a step further and a molecule of water is eliminated with the formation of unsaturated compounds. The distinction made here between reactions

of condensation and synthesis is a practical rather than a rigorously logical differentiation; in reactions of synthesis new carbon-to-carbon linkages are formed.*

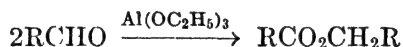
In their reactions of synthesis, aldehydes display greater versatility than ketones. Aldehydes will undergo reactions of synthetic value with themselves, with other aldehydes, with ketones, and with other classes of unsaturated compounds. The course of the reaction between two molecules of an aldehyde depends both upon the structure of the aldehyde involved and upon the condensing agent employed. Thus, if an aldehyde such as benzaldehyde which has no α -hydrogen atoms is treated with cyanide ion, certain metals, or ultra-violet light, a benzoin is formed.⁶³



The reaction is reversible,⁶⁴ and it is possible to prepare mixed benzoin by the interaction of two different aldehydes.⁶⁵ None of the mechanisms suggested for the reaction has gained general acceptance. If, instead of cyanide ion, strong alkali is employed, the Cannizzaro reaction takes place.⁶⁶ In this reaction one molecule of aldehyde is oxidized to the corresponding acid while the second is reduced to a primary alcohol.



The presence of peroxides is essential.⁶⁷ A crossed Cannizzaro reaction using formaldehyde and an aromatic aldehyde offers a convenient method of reducing the aromatic aldehyde essentially quantitatively to the corresponding primary alcohol.⁶⁸ Still a third variant is the Tischenko reaction whereby two molecules of an aldehyde, which may or may not contain α -hydrogen atoms, are converted to an ester by the use of an alkoxide catalyst.⁶⁹



* Where no distinction is desirable, it is not uncommon to find the term "condensation" applied to reactions resulting in a new carbon-carbon linkage.

⁶³ Schorigin, Issaguljanz, and Gussewa, *Ber.*, **66**, 1431 (1933); Wöhler and Liebig, *Ann.*, **3**, 276 (1832).

⁶⁴ Smith, *Ber.*, **26**, 65 (1893); Anderson and Jacobson, *J. Am. Chem. Soc.*, **45**, 836 (1923); Buck and Ide, *ibid.*, **53**, 2350, 2784 (1931).

⁶⁵ Buck and Ide, *ibid.*, **52**, 220, 4107 (1930).

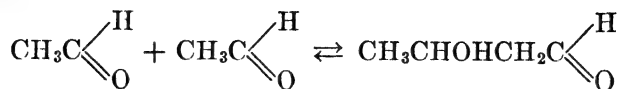
⁶⁶ Delépine and Horeau, *Bull. soc. chim.*, [5] **4**, 1524 (1937); Eitel and Lock, *Monatsh.*, **72**, 410 (1939).

⁶⁷ Kharasch and Foy, *J. Am. Chem. Soc.*, **57**, 1510 (1935).

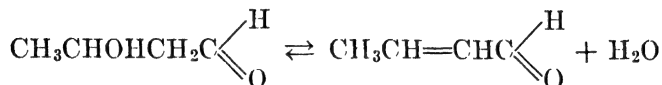
⁶⁸ Davidson and Bogert, *ibid.*, **57**, 905 (1935).

⁶⁹ Tischenko, *J. Chem. Soc.*, **92**, 182, 282, 284 (1907).

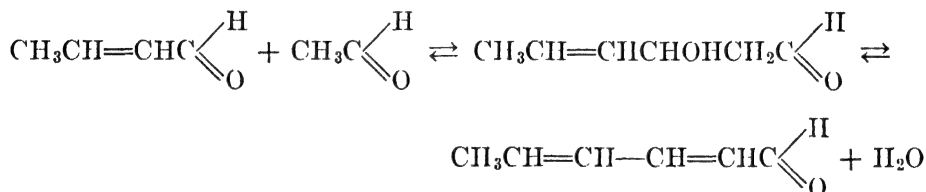
When an aldehyde having an α -hydrogen atom is treated with acids or bases aldolization takes place.



This first step is easily reversible. A second step, loss of water, which is brought about by the same catalysts, is also, but less readily, reversible.

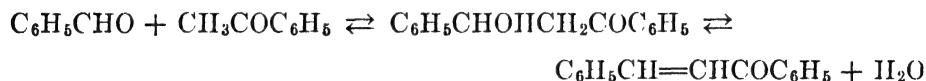


The unsaturated aldehyde formed as a result of aldolization can react with another molecule of aldehyde.

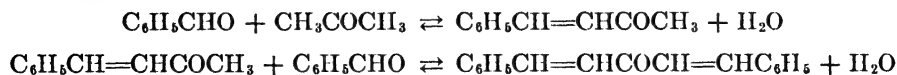


Progressive aldolization of this type which takes place in the presence of strong bases leads eventually to aldehyde resins.

The term aldolization need not be limited to the reaction between two molecules of an aldehyde. It can equally well be applied to all those reactions of synthesis which involve the addition to a carbonyl compound of an unsaturated compound containing an α -hydrogen atom. The primary hydroxyl-containing addition products are seldom isolated, however, except in the reaction between two molecules of an aldehyde. When the two components are an aldehyde and a ketone, the product is usually an unsaturated ketone.

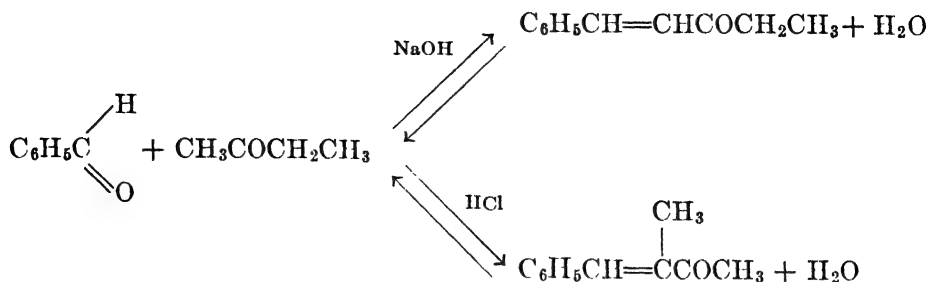


When two α -positions are available in the ketone both may usually be made to react and often both the possible products can be obtained.

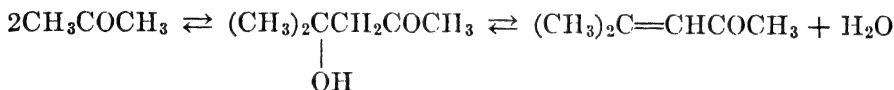


When an unsymmetrical ketone is employed, the course of the reaction can be controlled by the choice of the catalyst.⁷⁰

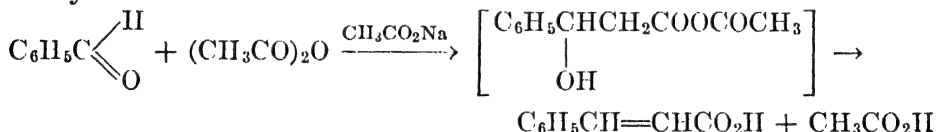
⁷⁰ Harries and Müller, *Ber.*, **35**, 966 (1902).



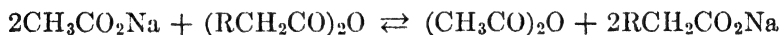
The carbonyl group in ketones is less reactive than that in aldehydes. As a consequence aldolization between two molecules of a ketone takes place but rarely. Exceptions are to be found in the most reactive ketones, acetone and cyclohexanone.



Aldolization followed by loss of water will also take place between an aldehyde and an acid anhydride—the Perkin synthesis—if the reaction is forced by sufficiently drastic conditions. The anhydride, perhaps as an enolate, adds to the aldehyde, the sodium salt serving as a basic catalyst.



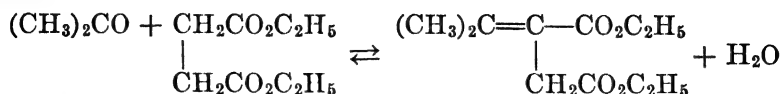
In support of this mechanism is the fact that the sodium salt can be replaced by other basic catalysts, certain amines, or inorganic salts such as potassium carbonate. Further, when the Perkin reaction is run with benzaldehyde, the salt of one organic acid and the anhydride of a different organic acid, or with equilibrated salt-anhydride mixtures, the ratios of cinnamic acid and substituted cinnamic acid formed are consistent with the equilibrium position of the interchange reaction



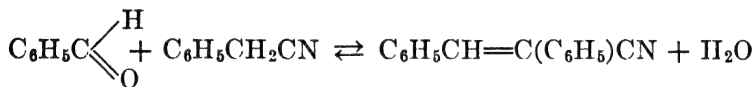
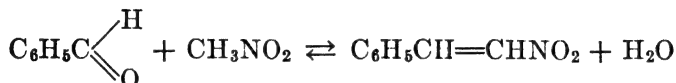
only when it is assumed that the anhydride condenses with the aldehyde. The interpretation just given is the original one advanced by Perkin; it was for many years believed, following Fittig, that the reaction involved addition of the sodium salt to the aldehyde and that the anhydride dehydrated the resulting addition product.*

* The interpretation given above is a result of the work of several chemists. An important contribution to this interpretation and an admirable survey of all the evidence is given by Breslow and Hauser, *J. Am. Chem. Soc.*, **61**, 786 (1939), and by Hauser and Breslow, *ibid.*, p. 793.

Aldehydes and occasionally ketones may undergo aldolization with esters. Metallic sodium or an alkoxide in an hydroxyl-free solvent is employed as a catalyst.

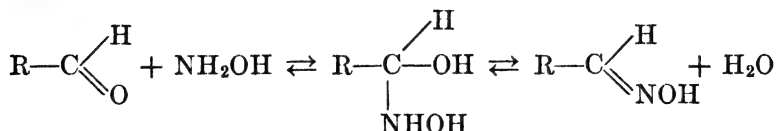


In the aldolization processes just described the carbonyl group has played a dual role; in one molecule it has served as the unsaturated group to which addition takes place, and in the second molecule it has served to activate a hydrogen atom in the α -position sufficiently to bring about addition. This second role of activating α -hydrogen atoms is also played by other unsaturated groups, and aldolization will take place, for example, between a carbonyl compound and an aliphatic nitro compound or a nitrile.*



At the beginning of this chapter it was stated that the activating effect of unsaturated groups on adjacent atoms was second in importance only to the ability of these unsaturated groups to undergo addition reactions. The variety and usefulness of the various aldolization reactions which have just been described serve to illustrate this statement.

The most important condensation reactions of the aldehydes and ketones are those with aniline, hydroxylamine, hydrazine, phenylhydrazine, and semicarbazide. The first of these gives rise to Schiff's bases; the remaining four furnish oximes, hydrazones, phenylhydrazones, and semicarbazones—derivatives frequently used for the isolation and identification of carbonyl compounds. The mechanism of these condensation reactions has been shown to involve addition of the reagent and subsequent elimination of water from the addition products. Both steps are reversible.



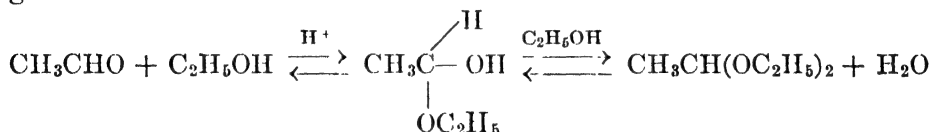
* For a discussion of the reaction mechanism, see Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937).

The chemical evidence for this mechanism is the isolation in favorable cases—chloral, *o*-nitrobenzaldehyde—of the intermediate addition products. The physical evidence is the fact that the rates of these condensation reactions for a series of carbonyl compounds are comparable with the rates of bisulfite addition to the same compounds. In Table I, p. 645, are shown the rates of oxime and phenylhydrazone formation for a comparison with the rates of bisulfite addition.

More precise measurements of the rates of carbonyl condensation reactions are to be found on p. 1049. Here it need only be noted that these more refined and extensive modern studies have shown that the rates of carbonyl addition reactions are not determined exclusively by such steric factors as the size and complexity of the groups present in the carbonyl compound.

The carbonyl group in esters reacts with hydroxylamine, hydrazine, ammonia, and similar compounds, but alcohol rather than water is eliminated in the second step of the process. The products of these reactions, hydroxamic esters, hydrazides, and amides, cannot be discussed here.

The addition of alcohol to aldehydes furnishes hemiacetals which are rarely isolated since they react with a second molecule of alcohol and give acetals.



Ketones seldom form acetals directly, but these derivatives may be obtained by condensation with an ester of orthoformic or orthosilicic acid.⁷¹



The addition of water to carbonyl compounds does not take place to an appreciable extent under ordinary conditions. From a few special compounds, for example chloral and mesoxalic acid, water addition products have been isolated.

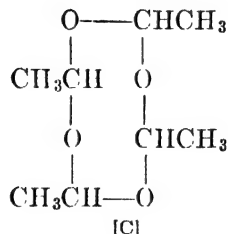
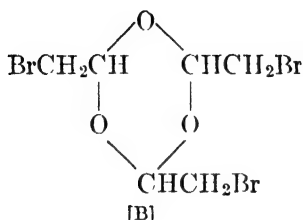
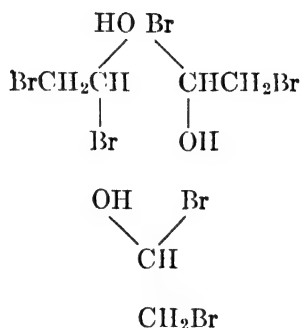
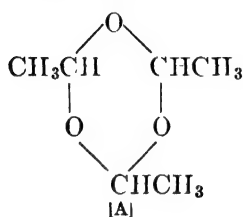
Many aldehydes and thioaldehydes when treated with mineral acids form two polymers. Ketones do not form such polymers, but thioketones do.⁷² The polymers of acetaldehyde are known as paraldehyde and metaldehyde. Mixed polymers of the paraldehyde type made from two different aldehydes are also known. The polymerization is reversible, and the equilibrium is reached rapidly in the presence of a catalyst.

⁷¹ Helferich and Hausen, *Ber.*, **57**, 795 (1924).

⁷² Schönberg, *Ber.*, **62**, 195 (1929).

Since the lower aldehydes are volatile and easily oxidized they are conveniently stored in their less sensitive polymerized forms.

Paraldehyde [A] contains a six-membered ring including three oxygen atoms. The mechanism of its formation probably involves addition of the catalyst to the carbonyl group followed by elimination in a different manner. In support of such a mechanism is the fact that the hydrogen bromide addition product of bromoacetaldehyde, which has been isolated, forms the corresponding paraldehyde [B] when treated with potassium acetate.⁷³



Measurements of the rates of paraldehyde formation from acetaldehyde show that the slowest step is a trimolecular reaction, which is to be expected since the loss of the catalyst in the final step involves three molecules.⁷⁴ Metaldehyde [C] is a tetramer, (CH₃CHO)₄, containing an eight-membered ring built up of alternate carbon and oxygen atoms with a hydrogen atom and a methyl group attached to each carbon atom.⁷⁵

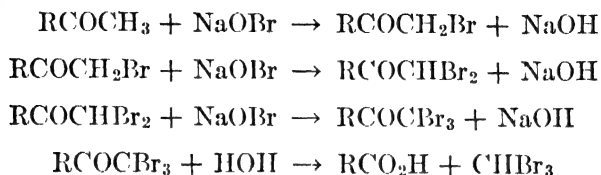
Halogens and Halogen Compounds. When certain aldehydes and ketones are treated with hypohalites, cleavage of the molecule with elimination of a haloform results. No intermediate products have been isolated from the reaction when it is carried out under the usual conditions, but by the selection of properly substituted ketones and under

⁷³ Stepanow, Preobraschensky, and Sehtschukina, *Ber.*, **59**, 2533 (1926).

⁷⁴ Hatcher and Kay, *Can. J. Research*, **7**, 337 (1932).

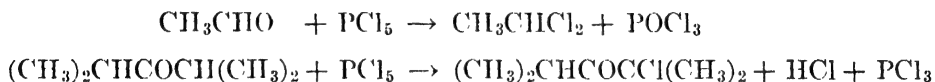
⁷⁵ Hantzsch and Oechalin, *Ber.*, **40**, 4341 (1907); Pauling and Carpenter, *J. Am. Chem. Soc.*, **58**, 1274 (1936).

carefully controlled conditions it has been shown that the reaction proceeds through stepwise halogenation followed by a chain cleavage of the resulting trihaloketones.⁷⁶

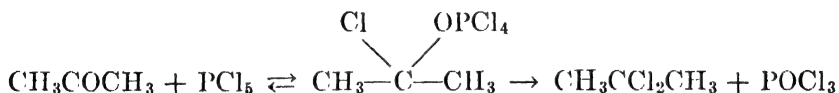


It is not certain that this mechanism applies equally well to water-soluble carbonyl compounds, for measurements of the rates of reaction of several substances of this type admit of other interpretations.⁷⁷

Phosphorus pentachloride reacts with many aldehydes and ketones. If the hydrocarbon radicals are simple, replacement of oxygen by chlorine takes place. Frequently unsaturated monochloro compounds, apparently formed by the loss of hydrogen chloride from the expected dichloro compounds, are found among the products. If the hydrocarbon residues are complex, the pentachloride sometimes reacts as trichloride and chlorine; an α -hydrogen atom is replaced and a chloroketone results. An excess of the halide has no effect on the carbonyl group.



As a consequence of the observation that phosphorus oxychloride was a product of the reaction when the oxygen atom of a carbonyl compound was replaced by chlorine, Straus suggested that the process involved addition of the pentachloride as $\text{Cl}-\text{PCl}_4$.⁷⁸



It should be noticed that the course of the reaction between carbonyl compounds and phosphorus pentachloride depends upon the activity of the carbonyl group as this activity is affected by the attached hydrocarbon residues. With phosphorus pentabromide, however, which is less stable than the pentachloride, carbonyl compounds give only products in which an α -hydrogen atom has been replaced by bromine.

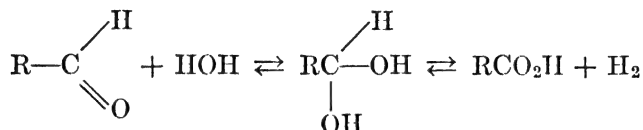
Oxidation. Aldehydes are easily oxidized to acids having the same number of carbon atoms; ketones are oxidized only with difficulty, and

⁷⁶ Fuson and Bull, *Chem. Rev.*, **15**, 275 (1934).

⁷⁷ Hatcher and Horwood, *Can. J. Research*, **11**, 378 (1934).

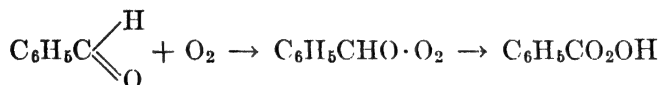
⁷⁸ Straus, *Ann.*, **393**, 235 (1912).

the carbon chain is broken. Since the oxidation of an aldehyde is accomplished by the same reagents which convert alcohols to aldehydes, the mechanism is probably the same. Wieland has suggested that the oxidation is in reality a dehydrogenation of the aldehyde hydrate and that the function of the oxidizing agent is to act as a hydrogen acceptor.⁷⁹ It is known that water adds to aldehydes and sometimes stable hydrates can be isolated. Wieland has found that in favorable cases dehydro-

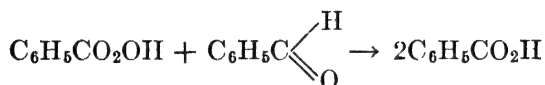


genation can be accomplished by means of certain hydrogen acceptors not usually considered to be oxidizing agents; methylene blue, azobenzene, indigo, and dibiphenyleneethylene have been so used. The reaction takes place in the absence of oxygen as long as the acceptor is present.

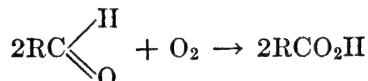
Autoxidation is a common phenomenon with aldehydes and is occasionally encountered with ketones.⁸⁰ With an aldehyde the end product of the reaction is the corresponding acid. Benzaldehyde adds oxygen to form an addition product which slowly yields perbenzoic acid.



The peracid, which is an oxidizing agent for many unsaturated compounds, converts a second molecule of aldehyde to acid.



The net result may be represented by the equation:



In this instance the perbenzoic acid presumably acts as a hydrogen acceptor.

Autoxidation, which is sensitive to catalysis by ozone,⁸¹ may be prevented with surprising ease by the use of a reducing agent as a

⁷⁹ Wieland, *Ber.*, **54**, 2353 (1921), and numerous later articles.

⁸⁰ Jenkins, *J. Am. Chem. Soc.*, **57**, 2733 (1935).

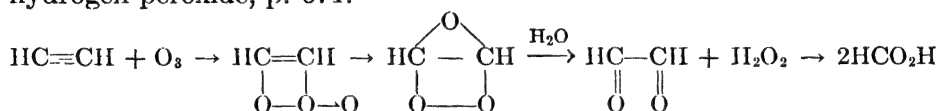
⁸¹ Briner and Perrottet, *Compt. rend. soc. phys. hist. nat. Genève*, **54**, 101 (1937) [*C. A.*, **32**, 6635 (1938)].

stabilizer. Hydroquinone is most commonly used, and as little as 0.001 per cent is effective. The same "antioxidants" are also effective in hindering or preventing the polymerization of many ethylenic compounds.

The Carbon-Carbon Triple Bond

The acetylenic linkage is characterized both by its ability to undergo addition reactions and by the fact that a hydrogen atom attached directly to an acetylenic carbon atom is sufficiently reactive to undergo replacement by metals. The formation and reactions of these metallic derivatives are discussed elsewhere (p. 525); it is necessary to note here merely that they are of use in the isolation and identification of acetylenic compounds and as synthetic tools.

In their addition reactions the acetylenes add two atoms of hydrogen or their equivalent to furnish products which contain an ethylenic linkage or a carbonyl group, depending upon the nature of the addend; the chemistry of the addition products is that of the doubly linked unsaturated system which they contain. In general the same reagents which add to ethylenic compounds will also add to acetylenic compounds so that a detailed review of the addition reactions can be dispensed with. Certain reactions, however, merit attention. The addition of hydrogen can be controlled so as to furnish ethylenic compounds and, by proper choice of the experimental procedure, either the *cis* ethylenes or the *trans* ethylenes can be obtained.⁸² Ozone adds to the acetylenic linkage, and the ozonides on decomposition furnish acids as a result of the cleavage of intermediate dicarbonyl compounds by hydrogen peroxide.⁸³ This should be compared with the behavior of α -diketones toward hydrogen peroxide, p. 671.



Unsymmetrical reagents, such as hydrogen bromide, add according to Markownikoff's rule; hydrogen bromide in the presence of peroxides undergoes abnormal addition.⁸⁴



Disubstituted acetylenes add unsymmetrical reagents in both possible ways.⁸⁵

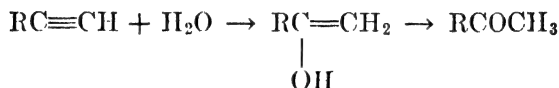
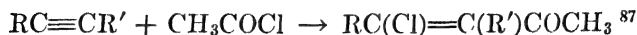
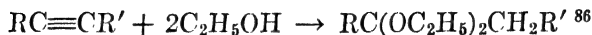
⁸² Campbell and Eby, *J. Am. Chem. Soc.*, **63**, 216 (1941).

⁸³ Hurd and Christ, *J. Org. Chem.*, **1**, 141 (1936); Jacobs, *J. Am. Chem. Soc.*, **58**, 2272 (1936).

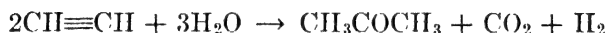
⁸⁴ Young, Vogt, and Nieuwland, *ibid.*, **58**, 1806 (1936).

⁸⁵ Bourguet, *Compt. rend.*, **178**, 1557 (1924).

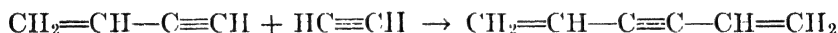
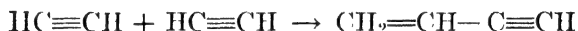
In the presence of suitable catalysts, a wide variety of oxygen-containing compounds add to acetylenes. The addition of alcohols furnishes ketals, acid chlorides furnish β -chloro unsaturated ketones, organic acids furnish alkenyl esters, and water furnishes ketones.



The hydration of acetylene, itself, can be directed so as to furnish either acetaldehyde or acetone.



Finally, acetylene in the presence of cuprous and ammonium chlorides will add a second molecule of acetylene or a molecule of a monosubstituted acetylene. The reaction makes possible the synthesis of substances containing both ethylenic and acetylenic linkages and when applied to acetylene itself furnishes vinylacetylene and divinylacetylene. The first of these products is the starting material for the preparation of one type of modern rubber substitute.⁸⁹



The Carbon-Nitrogen Double Bond

The unsaturation represented by the carbon-nitrogen double bond is found in aldimines, ketimines, and Schiff's bases and in oximes, hydrazones, and semicarbazones. In spite of the frequency with which such azomethines are encountered, relatively little study has been made of the behavior of the carbon-nitrogen double bond *per se*.

⁸⁶ Killian, Hennion, and Nieuwland, *J. Am. Chem. Soc.*, **58**, 80 (1936).

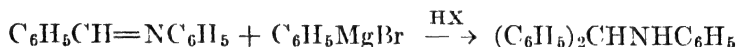
⁸⁷ Kroeger, Sowa, and Nieuwland, *J. Org. Chem.*, **1**, 163 (1936).

⁸⁸ Hennion and Nieuwland, *J. Am. Chem. Soc.*, **56**, 1802 (1934).

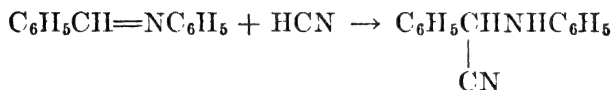
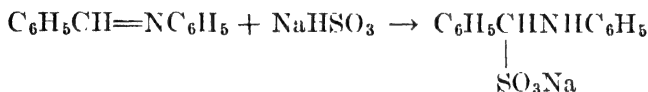
⁸⁹ Nieuwland, Calcott, Downing, and Carter, *ibid.*, **53**, 4197 (1931). "Collected papers of W. H. Carothers on Polymerization," edited by Mark and Whithy, Interscience Publishers, New York (1940).

Aldimines, ketimines, and Schiff's bases may be considered as substitution products of the hypothetical condensation product of ammonia and formaldehyde, $\text{CH}_2=\text{NH}$. Simple aldimines, $\text{RCH}=\text{NH}$, and Schiff's bases derived from formaldehyde, $\text{CH}_2=\text{NR}$, are unknown in the monomolecular state. One monomolecular aldimine and one monomolecular Schiff's base derived from formaldehyde have been described. They are readily hydrolyzed and reduced.⁹⁰ Polymeric aldimines and Schiff's bases are hydrolyzed with great ease by acids to form an aldehyde and ammonia or an amine, and they are easily reduced to primary or secondary amines. Monomolecular ketimines⁹¹ and Schiff's bases derived from aldehydes other than formaldehyde have been prepared; they too are readily hydrolyzed and reduced.

Schiff's bases of the type $\text{RCH}=\text{NR}$, for example benzalaniline, have been studied in some detail. Their behavior in addition reactions is reminiscent more of carbonyl compounds than of ethylenic compounds. These azomethines will add the Grignard reagent and organolithium compounds; the hydrocarbon residue adds to carbon.⁹²



They will add sodium bisulfite,⁹³ and hydrogen cyanide.⁹⁴ The bisulfite



addition product has been formulated as a sulfonic acid by analogy with the bisulfite addition products of carbonyl compounds. It is described in the literature as a sulfite ester. Schiff's bases add organic compounds containing an active α -hydrogen atom by a process which is analogous to aldolization,⁹⁵

⁹⁰ (a) Kohler and Drake, *J. Am. Chem. Soc.*, **45**, 1281 (1923); (b) Kohler and Blatt, *ibid.*, **50**, 1220 (1928).

⁹¹ Moureu and Mignonac, *Ann. chim.*, [9] **14**, 322 (1920).

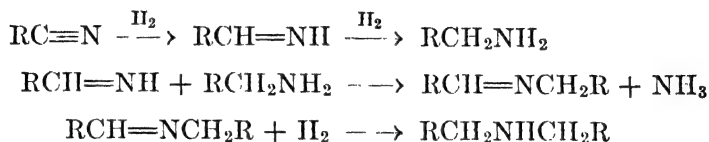
⁹² Busch, *Ber.*, **37**, 2691 (1904); Gilman and Kirby, *J. Am. Chem. Soc.*, **55**, 1265 (1933). (See, however, p. 688.)

⁹³ Ekeley and Swisher, *Rec. trav. chim.*, **48**, 1052 (1929).

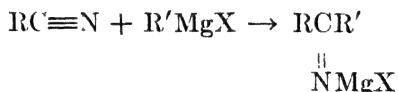
⁹⁴ Miller and Plöchl, *Ber.*, **31**, 2700 (1898).

⁹⁵ Mayer, *Bull. soc. chim.*, [3] **33**, 157, 395 (1905); Snyder, Kornberg, and Romig, *J. Am. Chem. Soc.*, **61**, 3556 (1939).

The addition of hydrogen, which may be brought about either catalytically or by metal combinations, would be expected to yield a primary amine. Actually there is a marked tendency to form secondary amines. The formation of secondary amines can be suppressed by employing acetic anhydride as a solvent when a platinum catalyst is used,⁹⁹ or by reducing with Raney nickel in the presence of ammonia.¹⁰⁰ The following mechanism has been suggested for the formation of a secondary amine on the reduction of a nitrile.¹⁰¹



The Grignard reagent adds to nitriles to form metallic derivatives of ketimines.⁹¹



In addition to the usual limitations resulting from an increase in the size or complexity of the group R, poor yields are frequently obtained because some of the nitrile reacts in the tautomeric imide form, $\text{RCH}=\text{C}=\text{NH}$. Many nitriles show evidence of this type of tautomerism in other reactions. The Grignard reagent in certain cases also brings about intermolecular addition; one molecule of nitrile, acting as HA, adds to the triple linkage of a second molecule to form an imine. Numerous organoalkali compounds are excellent catalysts for this reaction.¹⁰²

The Nitro Group

In the chemistry of the nitro group the activating influence of the unsaturated group on α -hydrogen atoms is of more importance than its addition reactions. In fact, the only addition reactions which need be considered are reduction and the addition of alkoxides.

Reduction of the nitro group can be brought about by a wide variety of reagents, and the course of the reduction is controlled by the structure of the nitro compound, the nature of the reagent, and the conditions under which the reaction is carried out. It suffices to point out that nitro compounds can always be reduced to primary amines and they can

⁹⁹ Carothers and Jones, *J. Am. Chem. Soc.*, **47**, 3051 (1925).

¹⁰⁰ Schwoegler and Adkins, *ibid.*, **61**, 3499 (1939).

¹⁰¹ v. Braun, Blessing, and Zobel, *Ber.*, **56**, 1988 (1923).

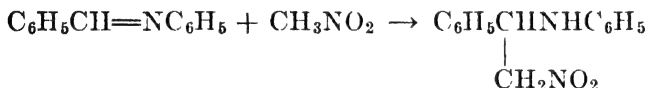
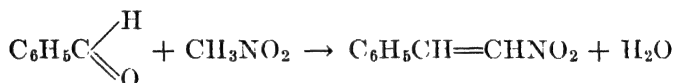
¹⁰² Ziegler and Ohlinger, *Ann.*, **495**, 84 (1932); Ziegler, Eberle, and Ohlinger, *Ann.*, **504**, 94 (1933).

sometimes be reduced to nitroso compounds, hydroxylamines, oximes, azoxy compounds, azo compounds, and hydrazo compounds. The chief practical importance of these reactions is in the field of aromatic chemistry where they lead to dye intermediates.

Organometallic compounds bring about reduction of the nitro group; the process is both complex and obscure (p. 504). Aromatic nitro compounds can be reduced to secondary amines;¹⁰³ aliphatic nitro compounds are reduced to dialkylhydroxylamines. In both reactions, addition as well as reduction takes place, and in the latter reaction one of the alkyl groups in the product is more complex than either the alkyl group of the reagent or the nitro compound.¹⁰⁴

Alkoxides convert nitro compounds containing an α -hydrogen atom to metallic derivatives of the *aci*-form, but if the alkaline treatment is prolonged the reaction goes past this stage. Nitro compounds which contain no α -hydrogen atoms will add a molecule of alkoxide.¹⁰⁵

Aldolization reactions involving a nitro compound which contains an α -hydrogen atom and carbonyl compounds or azomethines are important in synthetic work. The reactions with formaldehyde, benzaldehyde, and benzalaniline are typical. (Compare also the addition of nitro compounds to conjugated systems, p. 679).



TWINNED OR CUMULATIVE DOUBLE BONDS

Five systems of twinned or cumulative double bonds, allenes, cumulenes, ketenes, isocyanates, and carbodiimides, require attention. Allene, $\text{CH}_2=\text{C}=\text{CH}_2$, and its derivatives offer little that is novel in the way of addition reactions. The two ethylenic linkages act independently of each other, and they add the same reagents which add to isolated ethylenic linkages.¹⁰⁶ The mode of addition is in accordance with Markownikoff's rule, and the addition is subject to the same influences from substituent groups which were observed with ethylenic

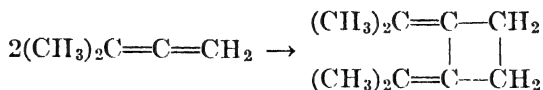
¹⁰³ Gilman and McCracken, *J. Am. Chem. Soc.*, **51**, 821 (1929).

¹⁰⁴ Bewad, *Ber.*, **40**, 3065 (1907).

¹⁰⁵ Meisenheimer, *Ann.*, **323**, 219 (1902).

¹⁰⁶ Acree and LaForge, *J. Org. Chem.*, **5**, 430 (1940).

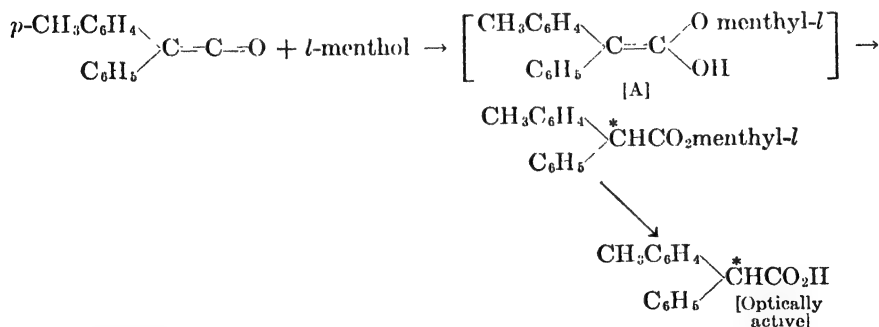
compounds. Simple allenes polymerize to yield, among other products, cyclobutane derivatives.¹⁰⁷



Alkyl-substituted allenes rearrange under the influence of alkali to furnish acetylenes,¹⁰⁸ and aryl-substituted allenes rearrange in an acid medium to furnish indenes.¹⁰⁹

Compounds containing several twinned ethylenic linkages, the cumulenes, $(\text{C}_6\text{H}_5)_2\text{C}=\text{C}=\text{C}=\text{C}(\text{C}_6\text{H}_5)_2$, are also known.¹¹⁰ These substances are colored, add hydrogen and halogens readily, react sluggishly with permanganate, and are stable toward molecular oxygen. They are inactive in the diene synthesis and should be contrasted with the conjugated polyenes described below on p. 693.

Ketene, $\text{CH}_2=\text{C}=\text{O}$, and its derivatives are among the most reactive of all unsaturated compounds in addition reactions.* Originally it was held that ketenes contained an abnormally reactive ethylenic linkage and that all addition reactions of ketenes were additions to the carbon-carbon double bond. It is true that the final products in all the addition reactions of ketenes contain the addend attached to what were the ethylenic carbon atoms. With two reagents, however, specific evidence has been presented to show that addition is to the carbonyl group and that ketonization of the primary addition product follows. The addition of *l*-menthol to phenyl-*p*-tolylketene followed by hydrolysis furnishes an optically active phenyl-*p*-tolylacetic acid. This is interpreted as showing the *sterically directed ketonization* of the primary addition product [A].¹¹¹



¹⁰⁷ Lebedeff, *J. Chem. Soc.*, **100**, 774 (1911).

¹⁰⁸ Favorsky, *J. prakt. Chem.*, [2] **37**, 417 (1888); [2] **44**, 208 (1891).

¹⁰⁹ Vorländer and Siebert, *Ber.*, **39**, 1030 (1906); Kohler, *Am. Chem. J.*, **40**, 220, 231 (1908).

¹¹⁰ Kuhn and Wallenfels, *Ber.*, **71**, 783, 1510 (1938).

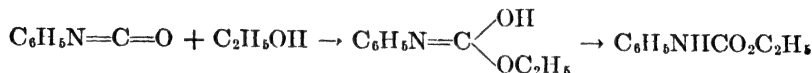
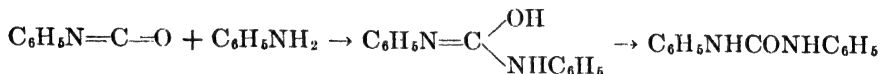
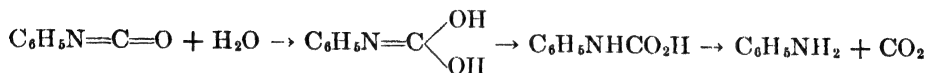
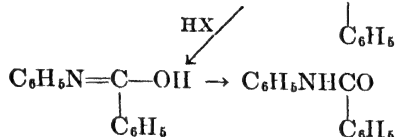
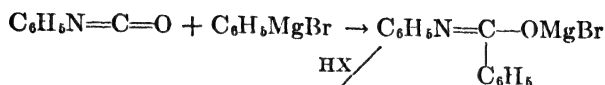
* The monograph by Staudinger, "Die Ketene," Enke, Stuttgart (1912), summarizes the early work on ketenes.

¹¹¹ Weiss, *Monatsh.*, **40**, 391 (1919).

¹¹⁴ Lewis, Ramage, Simonsen, and Wainwright, *J. Chem. Soc.*, 1837 (1937); Bergmann and Blum-Bergmann, *ibid.*, 727 (1938); Smith, Agre, Leekley, and Prichard, *J. Am. Chem. Soc.*, **61**, 7 (1939).

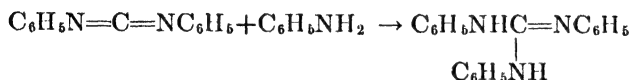
Ketenes do not take part in the diene synthesis (p. 685), but they do add acetylenes to give substituted α -naphthols.¹¹⁵

It is probable that the addition of HA reagents to the twinned double bonds in isocyanates follows the same course as the addition of these reagents to ketenes.¹¹⁶



Because they furnish characteristic solid derivatives by interaction with alcohols and amines the isocyanates are used for the identification of these two classes of compounds.

Twinned double bonds and characteristic activity in addition reactions are also found in the carbodiimides—a group of compounds which has been known for many years¹¹⁷ but which has become available for study and use relatively recently.¹¹⁸ Carbodiimides add, among other reagents, amines to form guanidines and acids to furnish acyl ureas.



Both reactions are obviously 1,2-additions.

¹¹⁵ Smith and Hoehn, *J. Am. Chem. Soc.*, **63**, 1181 (1941).

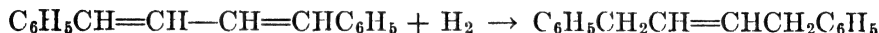
¹¹⁶ Gilman and Kinney, *ibid.*, **46**, 493 (1924).

¹¹⁷ Schall, *J. prakt. Chem.*, [2] **64**, 261 (1901); Busch, Blume, and Pungs, *ibid.*, [2] **79**, 513 (1909).

¹¹⁸ Zetysche and collaborators, *Ber.*, **71**, 1088 (1938), and several later articles; Schmidt and collaborators, *Ber.*, **71**, 1933 (1938); **73**, 286 (1940).

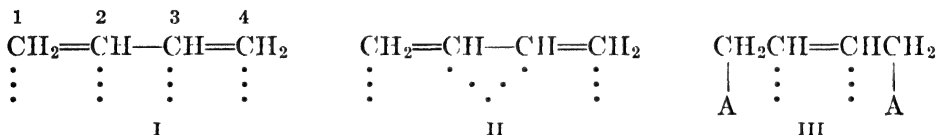
CONJUGATED SYSTEMS OF MULTIPLE LINKAGES

Relatively early in the development of organic chemistry abnormalities were observed in the course of certain of the addition reactions of substances which contained alternate single and multiple linkages. Thus, to use a comparatively recent example, when one mole of hydrogen is added to 1,4-diphenylbutadiene, addition takes place not at either of the ethylenic linkages but instead at the ends of the conjugated system.¹¹⁹



This type of addition is termed conjugate addition.¹²⁰ In an important article published in 1899, Thiele assembled many of the earlier data on conjugate addition, presented new evidence to show that many addition reactions not ordinarily considered so were conjugate, and proposed the theory of partial valence to account for the phenomenon.¹²¹

In Thiele's theory the initial assumption is made that not all the available affinity is used by a double bond between two atoms: the unused affinity on each atom is called a partial valence and is represented graphically by dotted lines as in I. In a conjugated system the partial valences present on the intermediate atoms (2 and 3 in formula I) neutralize each other so that the effective unsaturation is localized at the ends of the system as shown in II. Addition to such a system will take place at the end atoms and, since the addend will require more affinity than is available from the partial valences, the double bonds will be broken, a new double bond will be formed, and the final product will be III.



Thiele's explanation of conjugate addition was eagerly adopted—so eagerly, indeed, that at first but scant attention was paid to the fact that, although the theory of partial valence requires 1,4-addition exclusively, many cases of 1,2-addition to conjugated systems were known. In order to reconcile the general theory with these exceptions, Hinrichsen modified it so as to take into consideration the nature of the sub-

¹¹⁹ Straus, *Ann.*, **342**, 256 (1905).

¹²⁰ Lutz, *J. Am. Chem. Soc.*, **51**, 3008 (1929). The converse of this process, 1,4-elimination to form a conjugated system, is frequently encountered, but a discussion of 1,4-elimination is beyond the scope of this chapter. Compare p. 108 of reference 121(a).

¹²¹ Thiele, *Ann.*, (a) **306**, 87 (1899); (b) **308**, 333 (1899); see, also, Michael, *J. Am. Chem. Soc.*, **59**, 744 (1937).

stituents attached to the conjugated system and the nature of the addend.¹²² More recent developments have supplied plausible electronic interpretations for the occurrence of both 1,2-addition and conjugate addition as well as for the frequently observed interconversion of 1,2- and 1,4-addition products.* Lack of space, as well as the fact that there is not complete agreement between various electronic explanations, prevents a discussion of these modern interpretations in this chapter. Instead a descriptive treatment of the chemical behavior of the more important types of conjugated systems will be presented, stressing those reactions in which conjugated systems behave differently from their component unsaturated groups. Some physical properties associated with conjugation are considered elsewhere (Chapter 23).

The Dienes and Enynes

Dienes can be reduced either catalytically or by means of metal combinations. When hydrogen and a catalyst are used reduction can always be made complete. Often, in the catalytic reduction of dienes, the rate of 1,4-addition of hydrogen to the conjugated system is sufficiently greater than the rate of 1,2-addition to the resulting isolated ethylenic linkage to permit the two steps in the reduction to be followed experimentally. With other dienes, however, this is not so, and, in the addition of one mole of hydrogen to dienes such as $\text{RCH}=\text{CH}-\text{CH}=\text{CHR}'$,
 $\begin{array}{cccc} 1 & 2 & 3 & 4 \end{array}$
 1,2- and 3,4- and 1,4- additions have been reported.¹²³ Sometimes, also, using one mole each of diene and hydrogen, there is formation of the completely reduced product at the same time that some of the diene is unattacked.

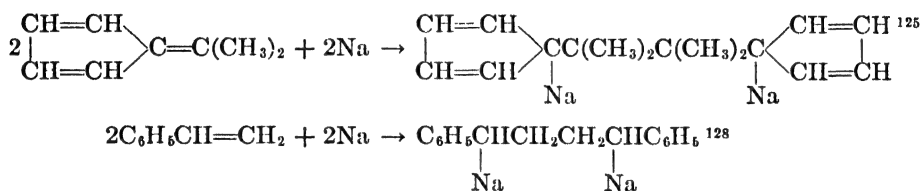
The addition of hydrogen to open-chain dienes by means of metal combinations is always conjugate, and, since the isolated ethylenic linkages thus formed are not reduced by metal combinations, reduction is never complete. The phenylated ethylenes (styrene, stilbene, and their analogs) behave as if the ethylenic linkage was conjugated with the nuclear double bonds, for these substances are reduced by metal combinations. The mode of hydrogen addition is 1,2, however, and phenylated ethanes are formed.

¹²² Hinrichsen, *Ann.*, **336**, 182 (1904).

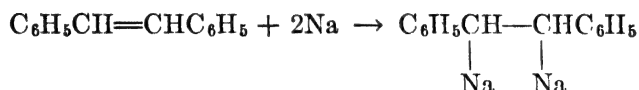
* For a discussion with leading references, see Waters, "Physical Aspects of Organic Chemistry," D. Van Nostrand, New York (1936), Chapter XV. Compare, also, Ingold, *Chem. Rev.*, **15**, 225 (1934); Baker, "Tautomerism," Routledge and Sons, Ltd., London (1934), pp. 248-262; and Muskat and Northrup, *J. Am. Chem. Soc.*, **52**, 4043 (1930). Compare also Chapter 25.

¹²³ (a) Lebedev and Yakubchik, *J. Chem. Soc.*, 823, 2190 (1928); (b) Dupont and Paquot, *Compt. rend.*, **205**, 805 (1937).

The addition of alkali metals is characteristic of conjugated ethylenic systems but not of isolated ethylenic linkages.* Simple dienes, such as butadiene, are polymerized by alkali metals and organoalkali compounds,¹²⁴ but terminally phenylated ethylenes add alkali metals 1,4.¹²⁵ Isoprene undergoes 1,4-ethylation with sodium and ethyl bromide¹²⁶ and adds triphenylmethyl 1,4.¹²⁷ If, in an ethylenic compound, one ethylenic carbon atom is either part of a crossed conjugated diene system or attached to an aromatic ring, alkali metal addition involving two moles of the unsaturated compound occurs.



If each ethylenic carbon atom in an ethylenic compound is attached to an aromatic ring system, the addition of alkali metal involves one molecule of the ethylenic compound.



Since the organoalkali addition-products on treatment with a hydrogen donor undergo replacement of metal by hydrogen the net result of the process is reduction.†

Because of the close correlation between the ability to add alkali metals and the susceptibility to reduction by metal combinations, it has been suggested that the latter reaction proceeds *via* metal addition followed by replacement of the metal in the resulting organoalkali compounds by hydrogen (p. 529).‡ Although doubtless a definite relation-

* For the addition of alkali metals to other unsaturated groups see reference 128 (b) and Chapter 5.

¹²⁴ Ziegler and Kleiner, *Ann.*, **473**, 57 (1929). Compare, however, Midgley and Henne, *J. Am. Chem. Soc.*, **51**, 1293 (1929).

¹²⁵ Houben-Weyl, "Die Methoden der organischen Chemie," Thieme, Leipzig (1924), Vol. IV, p. 966.

¹²⁶ Ziegler and Bähr, *Ber.*, **61**, 253 (1928).

¹²⁷ Conant and Scherp, *J. Am. Chem. Soc.*, **53**, 1941 (1931).

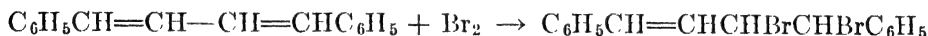
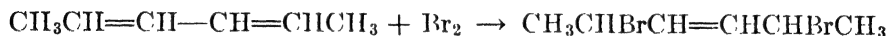
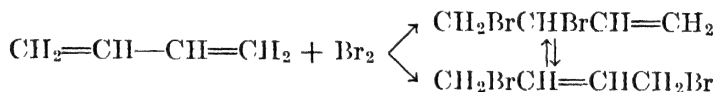
¹²⁸ Schlenk and Bergmann, (a) *Ann.*, **463**, 1 (1928); (b) *Ann.*, **464**, 22 (1928). Smith and Hoehn, *J. Am. Chem. Soc.*, **63**, 1184 (1941).

† The same reduction products can be obtained from the action of aluminum chloride and benzene on ethylenic compounds which contain one aromatic group on each ethylenic carbon atom. Alexander and Fuson, *J. Am. Chem. Soc.*, **58**, 1745 (1936).

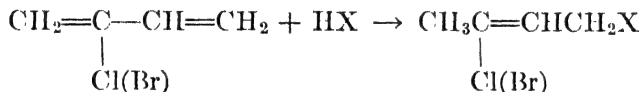
‡ Compare reference 51; also Carothers, *J. Am. Chem. Soc.*, **46**, 2226 (1924); and Hückel, "Theoretische Grundlagen der organischen Chemie," Akad. Verlags., Leipzig (1931), Vol. I, pp. 368-374.

ship exists between the addition of an alkali metal and reduction by metal combinations, it is probably not so simple as has been suggested, for in many cases the product of reduction by metal combinations is quite different from that obtained by metal addition and replacement. Thus styrene on reduction by metal combinations furnishes ethylbenzene, but on addition of alkali metal and subsequent replacement of the metal by hydrogen it furnishes 1,4-diphenylbutane.

The addition of halogens to dienes¹²⁹ may give rise to 1,2- or 3,4- or 1,4-addition products. In some cases mixtures of products are formed and in others the 1,2- and 1,4-products are in equilibrium with each other. These possibilities are illustrated by the following reactions.



The halogen acids add to dienes and enynes. In the most carefully studied cases, those of the 2-halobutadienes and vinylacetylene, addition is always conjugate.¹³⁰



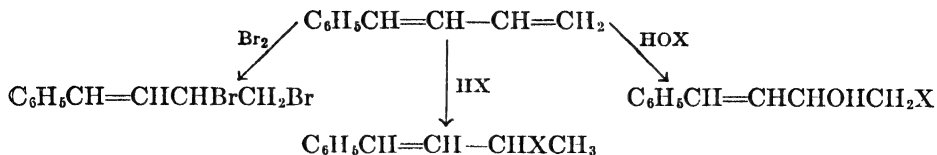
With 1-phenylbutadiene the reactions are not so clear cut, but the principal products are the result of 3,4-addition.*¹³¹

¹²⁹ (a) Butadiene: Farmer, Lawrence, and Thorpe, *J. Chem. Soc.*, 729 (1928); Muskat and Northrup, *J. Am. Chem. Soc.*, **52**, 4043 (1930). (b) Isoprene: Jones and Williams, *J. Chem. Soc.*, 829 (1934). (c) 2,3-Dimethylbutadiene: Kondakow, *J. prakt. Chem.*, **62**, 166 (1900). (d) 1,4-Dimethylbutadiene: Farmer, Lawrence, and Scott, *J. Chem. Soc.*, 510 (1930). (e) 2,3-Di-*t*-butylbutadiene: Backer, *Rec. trav. chim.*, **58**, 643 (1939). (f) 1,1,4,4-Tetramethylbutadiene: Prévost, *Compt. rend.*, **184**, 460 (1927). (g) 1-Phenylbutadiene: Muskat and Huggins, *J. Am. Chem. Soc.*, **51**, 2496 (1929). (h) 2,3-Diphenylbutadiene: Allen, Eliot, and Bell, *Can. J. Research*, **17B**, 75 (1939). (i) 1,4-Diphenylbutadiene: Straus, *Ber.*, **42**, 2867 (1909).

¹³⁰ Carothers, Williams, Collins, and Kirby, *J. Am. Chem. Soc.*, **53**, 4203 (1931); Carothers, Bercht, and Collins, *ibid.*, **54**, 4066 (1932); Carothers, Collins, and Kirby, *ibid.*, **55**, 786 (1933).

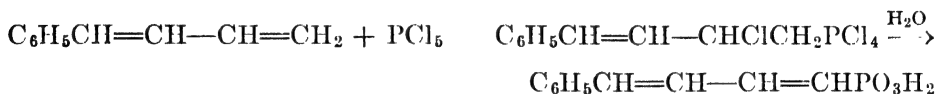
* For information about the addition of halogen and halogen acids to a wider variety of dienes than can be considered here, the reader is referred to the following articles: Farmer and collaborators, beginning with *J. Chem. Soc.*, 1570 (1926); Muskat and collaborators, beginning with *J. Am. Chem. Soc.*, **51**, 2496 (1929); Carothers and collaborators, beginning with *J. Am. Chem. Soc.*, **53**, 4203 (1931); Kharasch and collaborators, *J. Org. Chem.*, **1**, 393 (1936); **2**, 489 (1937). Compare also Staudinger, Kreis, and Schilt *Helv. Chim. Acta*, **5**, 743 (1922); Ruzicka and Schinz, *ibid.*, **23**, 960 (1940).

¹³¹ Muskat and Huggins, *J. Am. Chem. Soc.*, **56**, 1239 (1934).

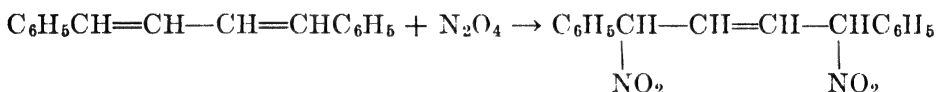


The addition of hypohalogenous acids and alkyl hypohalites to dienes is 1,2.¹³²

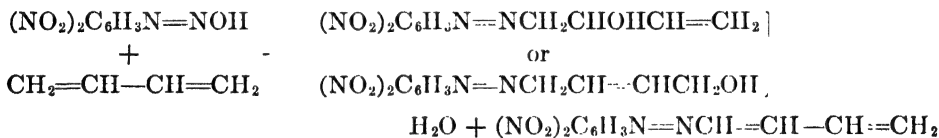
Phosphorus pentachloride adds to a limited number of dienes and styrenes, the latter again behaving as if the ethylenic linkage were conjugated with the aromatic nucleus. The addition is always to a terminally unsubstituted ethylenic linkage, and, since the addition products lose hydrogen chloride and are hydrolyzed to phosphinic acids, the over-all reaction is the replacement of an atom of hydrogen.¹³³



Among the nitrogenous addends to dienes should be mentioned the oxides of nitrogen and aromatic diazonium compounds. Oxides of nitrogen add 1,4 to 1,4-diphenylbutadiene, but both 1,2 and 1,4 to 2,3-diphenylbutadiene.¹³⁴



In the reaction between diazonium compounds and butadiene, evidence is not available to decide between 1,2- and 1,4-addition.¹³⁵



Hydrogen peroxide adds 1,4 to cyclopentadiene; simultaneously a tetrol resulting from the addition of two moles of peroxide is formed.¹³⁶

¹³² Abragam and Deux, *Compt. rend.*, **205**, 285 (1937); Petrov, *J. Gen. Chem. (U.S.S.R.)*, **8**, 131 (1938) [*C. A.*, **32**, 5369, 5370 (1938)]; *ibid.*, **10**, 819 (1940) [*C. A.*, **35**, 2112 (1941)].

¹³³ Bergmann and Bondi, *Ber.*, **63**, 1158 (1930); *Ber.*, **64**, 1455 (1931).

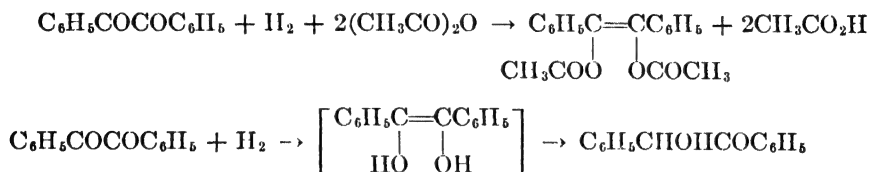
¹³⁴ Wieland and Stenzl, *Ber.*, **40**, 4825 (1907); *Ann.*, **360**, 299 (1908); Allen, Eliot, and Bell, *Can. J. Research*, **17B**, 75 (1939).

¹³⁵ Meyer, Irschlick, and Schlösser, *Ber.*, **47**, 1741 (1914).

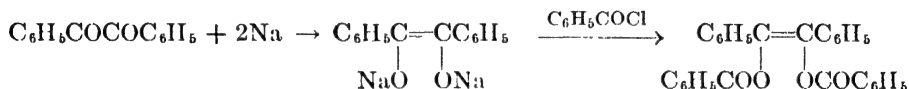
¹³⁶ Milas and Maloney, *J. Am. Chem. Soc.*, **62**, 1841 (1940).

1,2-Diketones

Conjugate addition is less frequently encountered with 1,2- or α -diketones than with other conjugated systems, for there are relatively few addends both parts of which will add to oxygen. Only hydrogen and the alkali metals add 1,4 to α -diketones. The reduction of benzil furnishes benzoin, apparently a result of 1,2-addition. Thiele, however, showed that this reduction was actually 1,4-addition of hydrogen followed by ketonization, for, by reducing the diketone in an acetylating medium, he was able to isolate the acetates of both stereoisomeric forms of the intermediate 1,4-addition product.¹²¹



Recently the enc-diol intermediates, themselves, have been isolated in analogous compounds.¹³⁷ Those α -diketones which cannot enolize will add sodium in the 1,4-positions; the metallic derivatives thus formed can be acylated with acid chlorides.¹³⁸



1,2-Diketones are cleaved with alkaline hydrogen peroxide.¹³⁹ The discoverers of this reaction suggested that it proceeded through the 1,4-addition of hydrogen peroxide as HO—OH, but later work indicates that the cleavage is a result of 1,2-addition of the reagent as H—OOH to a single carbonyl group.¹⁴⁰

The conjugated systems considered up to this point have, with the exception of the enynes, been made up of two or more similar unsaturated groups. The most frequently encountered and the most thoroughly studied conjugated systems, however, are those which contain two different unsaturated groups, and most of the remainder of this chapter is given over to the discussion of this kind of conjugated system. Nearly all substances containing a conjugated system which includes an oxygen atom show halochromism, the property of forming with strong acids

¹³⁷ Fuson and Corse, *ibid.*, **61**, 975 (1939); Fuson, Corse, and McKeever, *ibid.*, p. 2010; Thompson, *ibid.*, p. 1281.

¹³⁸ Kohler and Baltzly, *ibid.*, **54**, 4015 (1932); Bachmann, *ibid.*, **56**, 963 (1934).

¹³⁹ Weitz and Scheffer, *Ber.*, **54**, 2327 (1921).

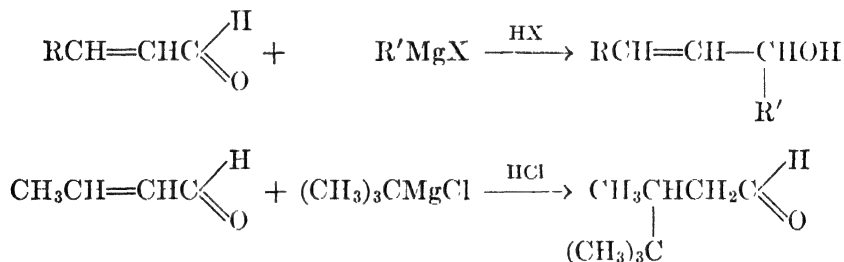
¹⁴⁰ Barnes and Lewis, *J. Am. Chem. Soc.*, **58**, 947 (1936).

colored saltlike products which are more or less readily decomposed by water.

α, β -Unsaturated Aldehydes and Ketones

Some reagents add 1,2 to the carbonyl group of α, β -unsaturated aldehydes and ketones; others add 3,4 to the ethylenic linkage; still others add 1,4 to the conjugated system, and a final group of reagents adds both 1,2 to the carbonyl group and 1,4 to the conjugated system.* Organomagnesium halides fall into this last category. With the Grignard reagent the mechanism of 1,4-addition has been established and the effect of substituents on the mode of addition has been determined. From the information available about the addition of the Grignard reagent, one can often predict whether other reagents will add and in what way they will add and one can draw reasonable inferences about the mechanism of addition. On account of the cardinal importance of the reactions between the Grignard reagent and α, β -unsaturated carbonyl compounds these reactions will be considered first.

α, β -Unsaturated aldehydes add the Grignard reagent 1,2 to the carbonyl group; the only exceptions so far described are the 1,4-additions of *tert.*-butyl- and *tert.*-amylmagnesium halides to crotonaldehyde.¹⁴¹

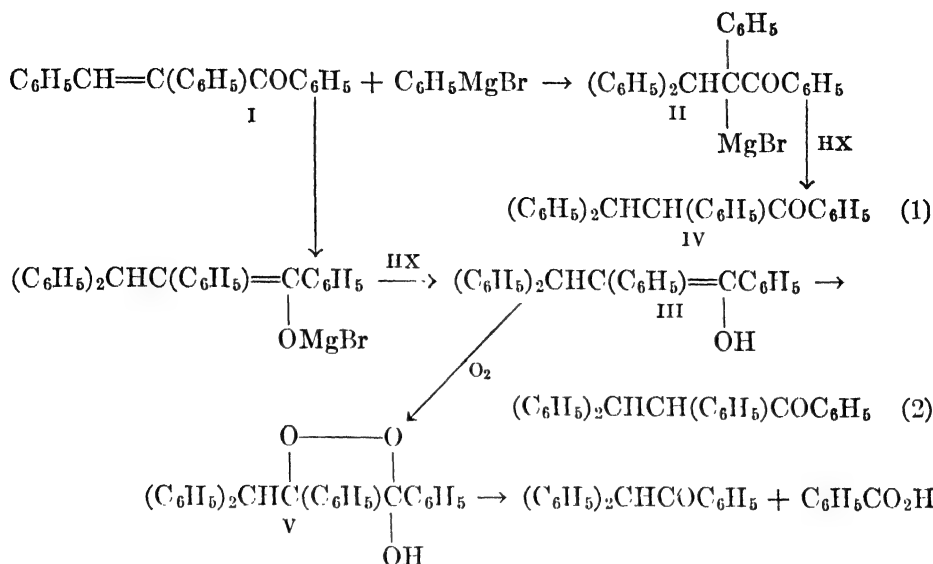


Unsaturated ketones furnish with the Grignard reagent saturated ketones or unsaturated alcohols or mixtures of both products.

The formation of unsaturated alcohols is obviously the result of 1,2-addition to the carbonyl group; the formation of saturated ketones may be due either to direct addition of the reagent to the ethylenic linkage (the reaction series 1) or to 1,4-addition of the reagent to the conjugated system followed by ketonization (the reaction series 2).

* Acetylenic ketones such as benzoylphenylacetylene, $\text{C}_6\text{H}_5\text{COC}\equiv\text{CC}_6\text{H}_5$, add the same reagents, with few exceptions, as do the ethylenic ketones, and the mode of addition is often similar. Recently α, β -unsaturated sulfones, $\text{C}_6\text{H}_5\text{CH}=\text{CHSO}_2\text{C}_6\text{H}_5$, have been prepared and studied. They, too, show many analogies with the ethylenic ketones. See Kohler and Potter, *J. Am. Chem. Soc.*, **57**, 1316 (1935).

¹⁴¹ Stevens, *J. Am. Chem. Soc.*, **57**, 1112 (1935).



The mechanism involving direct addition to the ethylenic linkage is improbable, for the Grignard reagent has never been observed to add to an ethylenic linkage that was not conjugated either with a carbonyl group or with a carbon-nitrogen double or triple linkage. Further, if direct addition were to take place, the magnesium halide derivative (II) with an unprotected carbonyl group should react with excess reagent to furnish a saturated tertiary alcohol. Positive proof that the formation of saturated ketones proceeds through 1,4-addition was presented by Kohler, who established the structures of the enolic 1,4-addition products.¹⁴² In the case of benzaldehydesoxybenzoin (I), the enol (III) is sufficiently stable to permit isolation, examination, and study of its conversion to the ketone (IV). The structure of the enol (III) is shown by the formation and decomposition of the peroxide (V).

The effect of substituents on the mode of addition of the Grignard reagent to α,β -unsaturated carbonyl compounds is shown by the data in Table III. It will be noted that as the activity of the carbonyl group decreases the amount of 1,4-addition increases. The mode of addition depends upon the number, kind, and positions of the substituents in the carbonyl compound and upon the group present in the Grignard

¹⁴² Kohler, *Am. Chem. J.*, **36**, 181 (1906). See, also, Kohler, *ibid.*, **37**, 369 (1907); Kohler and Mydans, *J. Am. Chem. Soc.*, **54**, 4667 (1932); Kohler, Tishler, and Potter, *ibid.*, **57**, 2517 (1935); reference 142. An earlier proof of addition, also due to Kohler, *Am. Chem. J.*, **31**, 642 (1904), and Kohler and Johnston, *ibid.*, **33**, 45 (1905), which was based on the replacement of $-\text{MgBr}$ in the addition product by reaction with benzoyl chloride, is no longer conclusive, for this type of replacement has been found to be unreliable. Kohler and Tishler, *J. Am. Chem. Soc.*, **54**, 1594 (1932).

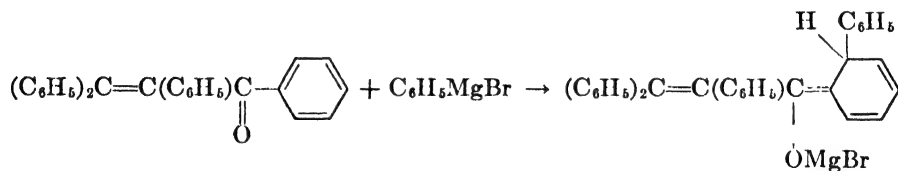
reagent.¹⁴³ Reaction medium and temperature usually have little effect. In the reaction between isophorone and methylmagnesium bromide, however, the addition of one mole per cent of cuprous chloride changes the course of the reaction from 90 per cent 1,2-addition to 7 per cent 1,2- and 82 per cent 1,4-addition.^{143a}

TABLE III¹⁴⁴

| Substance | Per Cent 1,4-Addition With | |
|---|--------------------------------------|--------------------------------------|
| | C ₆ H ₅ MgBr * | C ₂ H ₅ MgBr * |
| $\text{C}_6\text{H}_5\text{CH}=\text{CHC}\begin{array}{l} \nearrow \text{H} \\ \searrow \text{O} \end{array}$ | 0 | 0 |
| $\text{C}_6\text{H}_5\text{CH}=\text{CHCOCH}_3$ | 12 | 60 |
| $\text{C}_6\text{H}_5\text{CH}=\text{CHCOCH}_2\text{CH}_3$ | 40 | 71 |
| $\text{C}_6\text{H}_5\text{CH}=\text{CHCOCH}(\text{CH}_3)_2$ | 88 | 100 |
| $\text{C}_6\text{H}_5\text{CH}=\text{CHCOC}(\text{CH}_3)_3$ | 100 | 100 |
| $\text{C}_6\text{H}_5\text{CH}=\text{CHCOC}_6\text{H}_5$ | 94 | 99 |
| $(\text{C}_6\text{H}_5)_2\text{C}=\text{CHCOC}_6\text{H}_5$ | 0 | 18 |
| $\text{C}_6\text{H}_5\text{CH}=\text{C}(\text{C}_6\text{H}_5)\text{COC}_6\text{H}_5$ | 100 | 100 |
| $\text{C}_6\text{H}_5\text{C}(\text{CH}_3)=\text{CHCOC}_6\text{H}_5$ | 44 | 41 |

* The remainder of the product is to be accounted for by 1,2-addition.

The completely phenylated ketone, diphenylbenzalacetophenone, does not react with the Grignard reagent under ordinary conditions. The forced reaction, at higher temperatures, results in 1,4-addition involving a phenyl group.¹⁴⁵



If addition involving the phenyl nucleus is blocked by the use of a mesityl group, the usual type of 1,4-addition results on forcing the reaction.¹⁴⁶

¹⁴³ Smith and Hanson, *J. Am. Chem. Soc.*, **57**, 1326 (1935); Colonge, *Bull. soc. chim.* [5] **2**, 754 (1935).

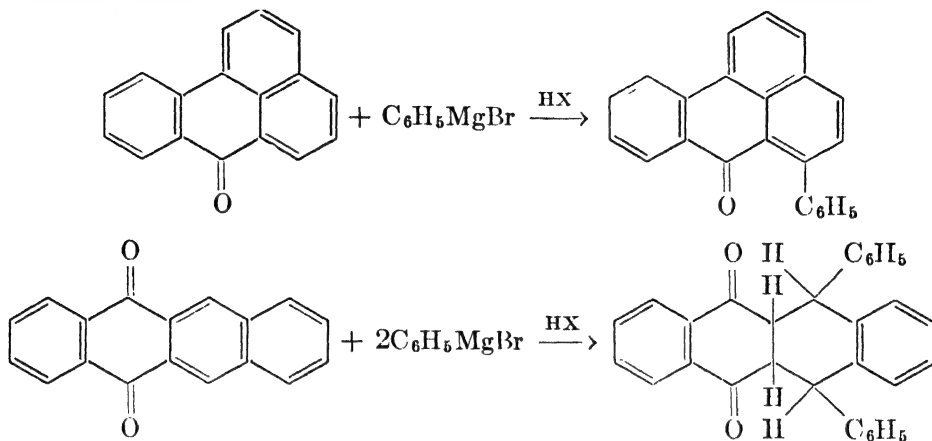
^{143a} Kharasch and Tawney, *J. Am. Chem. Soc.*, **63**, 2308 (1941).

¹⁴⁴ Kohler, *Am. Chem. J.*, **38**, 511 (1907).

¹⁴⁵ Kohler and Nygaard, *J. Am. Chem. Soc.*, **52**, 4128 (1930).

¹⁴⁶ Kohler and Barnes, *ibid.*, **55**, 690 (1933).

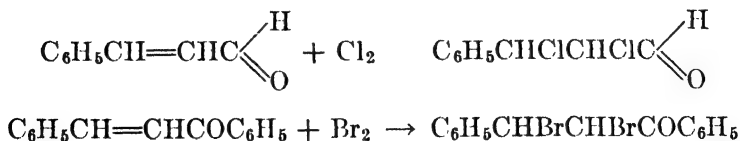
Similar 1,4-additions involving a cyclic double bond are found in polynuclear ketones. Benzanthrone and naphthacenequinone add certain Grignard reagents in the 1,4-position.¹⁴⁷ With the quinone the primary product, a tetrahydroaromatic derivative, can be isolated.



The behavior of a variety of phenylmetallic compounds toward benzalacetophenone has been investigated.¹⁴⁸ As the reactivity of these phenylmetallic compounds decreases, the amount of 1,4-addition increases. The very reactive compounds, diphenylcalcium and phenylpotassium, give 1,2-addition only. With α,β -unsaturated aldehydes and ketones the organozinc compounds furnish products similar to those obtained with the Grignard reagent.¹⁴⁹

The information about the addition of organomagnesium halides to α,β -unsaturated carbonyl compounds being available, the other reactions of these unsaturated compounds may now be discussed. Whenever possible, cinnamic aldehyde, $\text{C}_6\text{H}_5\text{CH}=\text{CHCHO}$, and benzalacetophenone, $\text{C}_6\text{H}_5\text{CH}=\text{CHCOC}_6\text{H}_5$, will be used to illustrate these reactions.

Considering first the reactions of the ethylenic linkage, it is to be noted that the halogens add to that linkage in the usual manner.



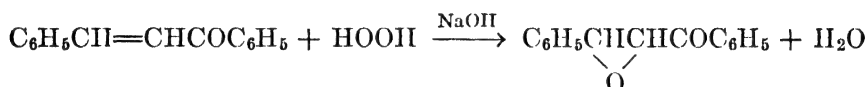
Most oxidizing agents convert cinnamic aldehyde to benzoic acid.

¹⁴⁷ Allen and Overbaugh, *ibid.*, **57**, 740, 1322 (1935); Allen and Gilman, *ibid.*, **58** 937 (1936); Allen and Bell, *ibid.*, **62**, 2408 (1940).

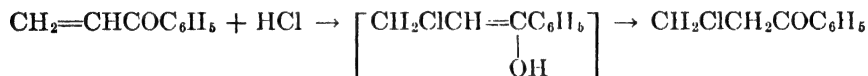
¹⁴⁸ Gilman and Kirby, *ibid.*, **63**, 2046 (1941).

¹⁴⁹ Kohler and Heritage, *Am. Chem. J.*, **43**, 475 (1910).

Atmospheric oxygen or silver oxide, however, furnishes cinnamic acid. Ozone gives benzaldehyde, benzoic acid, and a polymer of glyoxal.¹⁵⁰ Benzalacetophenone is oxidized to benzoic acid by most oxidants, including ozone, but nitric acid oxidation furnishes some benzoylformic acid.¹⁵¹ Perbenzoic acid, which forms epoxides with isolated ethylenic linkages,⁹ rarely attacks α,β -unsaturated carbonyl compounds, while alkaline hydrogen peroxide and sodium peroxide, which are without effect on isolated ethylenic linkages, form epoxides with α,β -unsaturated ketones.¹³⁹



The halogen acids do not add to all α,β -unsaturated carbonyl compounds. Where addition does take place, usually a single product is formed and in this product the halogen is attached to the β -carbon atom; see, however, phenylpropionic acid, p. 682. The mechanism of addition is in all probability 1,4 with hydrogen adding to oxygen, followed by ketonization.



In the presence of aluminum chloride or sulfuric acid, benzene adds reversibly to α,β -unsaturated ketones.¹⁵² The addend appears on the ethylenic carbon atoms. The mechanism is not clear.

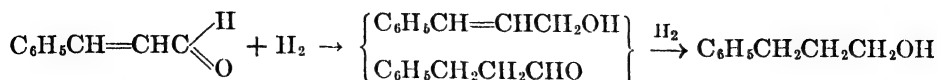
Hydrogen and diphenylketene add both to isolated ethylenic linkages and to carbonyl groups. When these two types of double bonds are conjugated, hydrogen may be added catalytically or by the use of metal combinations. By either method, α,β -unsaturated aldehydes give saturated aldehydes, unsaturated alcohols, and saturated alcohols. Only rarely is bimolecular reduction of an unsaturated aldehyde encountered.¹⁵³ Selective reduction of the carbonyl group to yield an unsaturated alcohol is accomplished by catalytic reduction with a promoter such as ferric chloride,⁵⁰ or by means of an aluminum alkoxide and an alcohol.⁵⁵

¹⁵⁰ Harries and Temme, *Ber.*, **40**, 169 (1907).

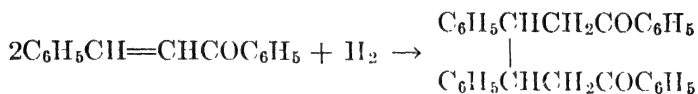
¹⁵¹ Claisen and Claparède, *Ber.*, **14**, 2465 (1881).

¹⁵² Kohler, *Am. Chem. J.*, **31**, 642 (1904); Vorländer and Friedberg, *Ber.*, **56**, 1144 (1923); Eaton, Black, and Fuson, *J. Am. Chem. Soc.*, **56**, 687 (1934).

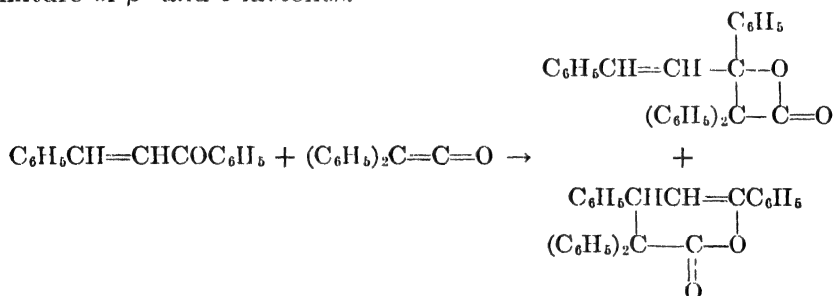
¹⁵³ Sörensen, Stene, and Samuelsen, *Ann.*, **543**, 137 (1940).



Unsaturated ketones can be reduced to saturated ketones by catalytic hydrogenation or to unsaturated alcohols by means of aluminum isopropoxide.¹⁵⁴ Reduction by means of metal combinations, however, leads primarily to bimolecular products.¹⁵⁵ The mechanism of the reduction to saturated ketones by catalytic hydrogen has been shown to be probably 1,4-addition; the corresponding reduction by metal combinations is definitely 1,4-addition.¹⁵⁶ In all likelihood the formation of the bimolecular products involves addition of hydrogen to oxygen followed by dimerization in the 4-position.



Diphenylketene adds both 1,2 and 1,4 to benzalacetophenone, giving a mixture of β - and δ -lactones.¹⁵⁷



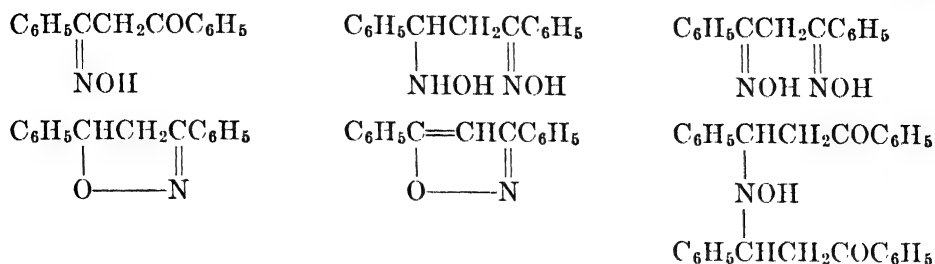
Of the reactions characteristic of the carbonyl group the addition of sodium bisulfite to unsaturated aldehydes and ketones may be considered first. Cinnamic aldehyde forms a bisulfite addition product just as other aldehydes do, but on prolonged treatment with the reagent the salt of a disulfonic acid is obtained. The explanation for this behavior is the following: the 1,2-addition of bisulfite to the carbonyl group to yield [A] is rapid and reversible, whereas the formation of the sulfonic acid through 1,4-addition is slow and irreversible. As a result the bisulfite addition product initially formed gradually disappears as the disulfonic acid accumulates.

¹⁵⁴ Arcus and Kenyon, *J. Chem. Soc.*, 698 (1938).

¹⁵⁵ Conant and Cutter, *J. Am. Chem. Soc.*, **48**, 1020 (1926); Harries and Hübner *Ann.*, **296**, 295 (1897).

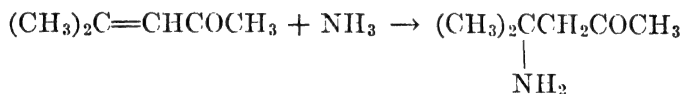
¹⁵⁶ Kohler and Thompson, *J. Am. Chem. Soc.*, **59**, 887 (1937).

¹⁵⁷ Staudinger, "Die Ketene," Enke, Stuttgart (1912), p. 64.

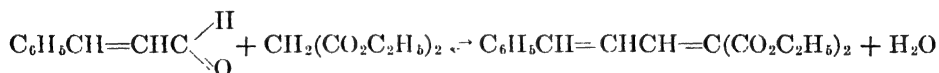


With methoxyamine instead of hydroxylamine, secondary reactions do not take place and the products are those resulting from addition to the ethylenic linkage, presumably through a 1,4-addition.¹⁶⁰

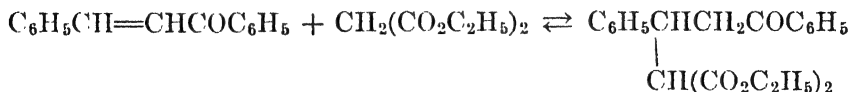
With α,β -unsaturated carbonyl compounds, ammonia and amines furnish products corresponding to addition to the ethylenic linkage. As in the reactions just described, complications may result from secondary reactions due to the active hydrogen atoms in the primary addition products.



Malonic, cyanoacetic, and acetoacetic esters, aliphatic nitro compounds, desoxybenzoin, and a host of other substances containing hydrogen atoms activated by adjacency to an unsaturated group, will react reversibly with α,β -unsaturated carbonyl compounds in the presence of a small amount of alkali.¹⁶¹ With α,β -unsaturated aldehydes 1,2-addition to the carbonyl group takes place; the reaction is analogous to the aldolization reactions of simple aldehydes.



With unsaturated ketones reaction does not always take place. A convenient generalization is that these reagents add when the Grignard reagent adds 1,4. The reagent adds as H and A, and A always appears attached to the β -carbon atom.¹⁶²



It is important to use only a small amount of alkali to prevent reversal of the addition and to avoid secondary reactions.¹⁶³ Thus, in

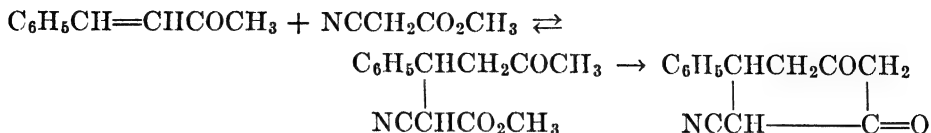
¹⁶⁰ Blatt, *J. Am. Chem. Soc.*, **61**, 3494 (1939).

¹⁶¹ Connor and McClellan, *J. Org. Chem.*, **3**, 570 (1939).

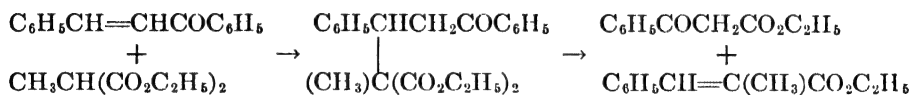
¹⁶² Vorländer, *Ann.*, **320**, 66 (1902).

¹⁶³ Kohler and P. Allen, *J. Am. Chem. Soc.*, **45**, 1987 (1923); Michael and Ross, *ibid.* **52**, 4598 (1930); **55**, 1632 (1933); Connor, *ibid.*, **56**, 2713 (1934).

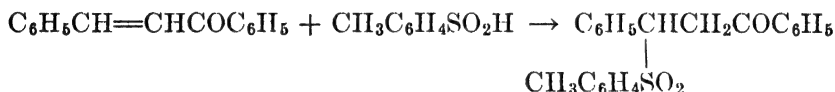
the presence of a small amount of alkali, cyanoacetic ester adds to benzalacetone, but with one equivalent of alkali the primary addition product is cyclized.



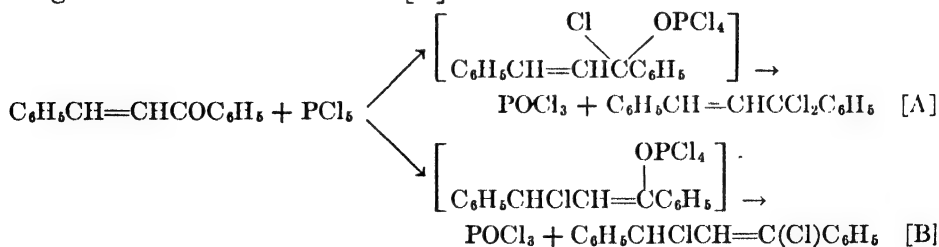
Frequently the primary addition product adds to a second molecule of ketone to form a "trimolecular" product. Reversal of the addition reaction does not always lead to the original products: the reaction between diethyl methylmalonate and benzalacetophenone using a mole of alcoholate furnishes ethyl benzoylacetate and ethyl α -methyl-cinnamate.¹⁶⁴ In this connection comparison should be made with the addition of malonic esters to α,β -unsaturated esters described on p. 682.



Thiophenol¹⁶⁵ and sulfinic acids¹⁶⁶ add 1,4 to unsaturated ketones as H and A, the hydrogen appearing on the α -carbon atom in the addition product.



The reactions of α,β -unsaturated ketones with phosphorus pentachloride and trichloride are difficult to classify. The pentachloride furnishes phosphorus oxychloride and oxygen-free unsaturated compounds containing chlorine.¹⁶⁷ The mechanism may be 1,2- or 1,4-addition. The product [B] obtained from benzalacetophenone corresponds to 1,4-addition, but a 1,2-addition product [A] would contain a system that is known to rearrange easily, and 1,2-addition followed by rearrangement would also furnish [B].



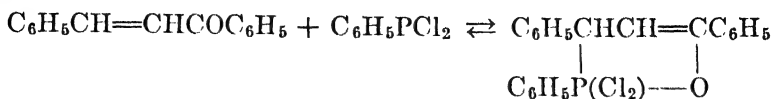
¹⁶⁴ Holden and Lapworth, *J. Chem. Soc.*, 2368 (1931).

¹⁶⁵ Posner, *Ber.*, **37**, 502 (1904); Ruhemann, *J. Chem. Soc.*, **87**, 17, 461 (1905).

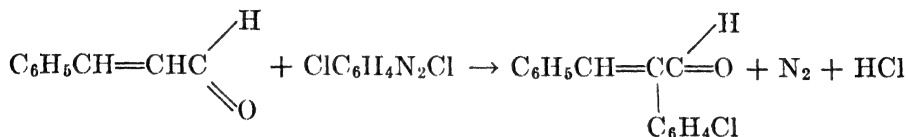
¹⁶⁶ Kohler and Reimer, *Am. Chem. J.*, **31**, 163 (1904).

¹⁶⁷ Straus, *Ann.*, **393**, 235 (1912); Conard, *J. Am. Chem. Soc.*, **62**, 1002 (1940).

In the reversible addition of phosphorus and organophosphorus halides, the addend does not dissociate; instead the phosphorus undergoes an increase in valence and cyclic products result.¹⁶⁸

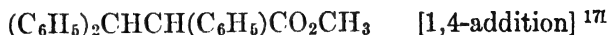
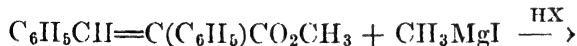
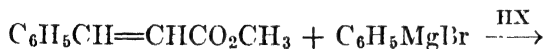
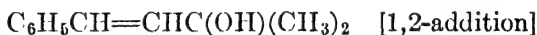
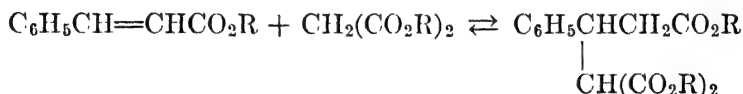


In the reaction between diazonium salts and some α,β -unsaturated carbonyl compounds, nitrogen is eliminated and an α -hydrogen atom is replaced by an aryl group.¹⁶⁹



α,β -Unsaturated Acids and Esters

Simple α,β -ethylenic and acetylenic acids, their derivatives and substitution products, closely resemble the corresponding unsaturated ketones in their chemical behavior. Many of the HA reagents which add to unsaturated carbonyl compounds add to the acids unless there is interference from the acidic hydrogen atom. The mode of addition can often be predicted fairly closely by analogy with the corresponding ketones.

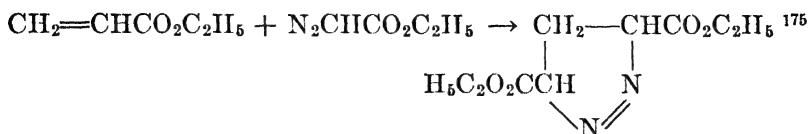


¹⁶⁸ Conant, *J. Am. Chem. Soc.*, **43**, 1705 (1921).

¹⁶⁹ Meerwein, Büchner, and van Emster, *J. prakt. Chem.*, **152**, 237 (1939).

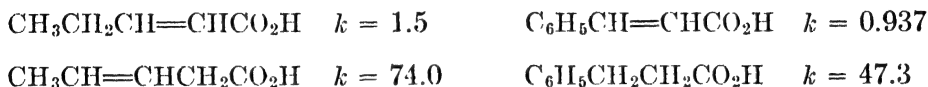
¹⁷⁰ Kohler and Heritage, *Am. Chem. J.*, **33**, 21 (1905).

¹⁷¹ Kohler and Heritage, *ibid.*, **33**, 153 (1905).



Aromatic diazonium salts react with α,β -unsaturated esters. Nitrogen is eliminated, and addition as $\text{Aryl} - \text{X}$ takes place, the aryl group adding to the α -carbon atom. With acetylenic acids a parallel reaction takes place, while with ethylenic acids the aryl group replaces an α -hydrogen atom and carbon dioxide is lost to furnish stilbenes.¹⁶⁹

Using the α,β -unsaturated acids it is possible by studying the rates of esterification to show that conjugation of a carboxyl group with an ethylenic linkage decreases the reactivity of the carboxyl group. Thus, for esterification under comparable conditions, the following results are available.¹⁷⁶



Similarly the effect of conjugation with a carboxyl group on the reactivity of an ethylenic linkage can be established by the determination of the rates of addition of bromine to unsaturated acids. Determination of these rates shows that the rate of bromine addition to an ethylenic linkage conjugated with a carboxyl group is much slower than to an isolated ethylenic linkage.

TABLE IV¹⁷⁷

| SUBSTANCE | BROMINE ADDITION |
|---|----------------------|
| | k 15° |
| $\text{CH}_3\text{CH}=\text{CHCO}_2\text{H}$ | 4.7×10^{-6} |
| $\text{CH}_3\text{CH}_2\text{CH}=\text{CHCO}_2\text{H}$ | 3.3×10^{-5} |
| $\text{CH}_3\text{CH}=\text{CHCH}_2\text{CO}_2\text{H}$ | 10.0 |

The addition of hypochlorous acid to ethylenic double bonds is also much retarded if the bonds are conjugated with a carboxyl group and the nature of the products is influenced by the proximity of the ethylenic linkage to the carboxyl group.¹⁷⁸ The acids $\text{CH}_3\text{CH}=\text{CHCH}_2\text{CH}_2\text{CO}_2\text{H}$ and $\text{CH}_3\text{CH}_2\text{CH}=\text{CHCH}_2\text{CO}_2\text{H}$ add hypochlorous acid readily and give mixtures of the two possible products, while the acid

¹⁷⁵ Buchner and co-workers, *Ann.*, **273**, 214 (1893); Auwers and Ungemach, *Ber.*, **66**, 1198 (1933).

¹⁷⁶ Sudborough and Gittins, *J. Chem. Soc.*, **95**, 315 (1909).

¹⁷⁷ Sudborough and Thomas, *ibid.*, **97**, 715, 2451 (1910).

¹⁷⁸ Bloomfield and Farmer, *ibid.*, 2062, 2072 (1932); Bloomfield, Farmer, and Hose, *ibid.*, 800 (1933); Farmer and Hose, *ibid.*, 962 (1933). See, also, reference 38.

$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CHCO}_2\text{H}$ combines with the same addend very slowly and gives only one product.



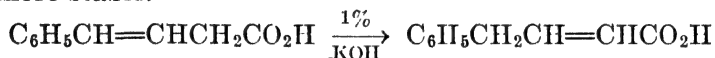
Such unidirectional addition of hypochlorous acid to α,β -unsaturated acids does not always take place, as the following data show, for this reagent is not of the HA type where H necessarily enters the molecule *via* oxygen.

TABLE V

| SUBSTANCE | PER CENT PRODUCT WITH OH ON β -CARBON ATOM* |
|--|--|
| $\text{CH}_3\text{CH}=\text{CHCO}_2\text{H}$ | 74 |
| $\text{CH}_2=\text{C}(\text{CH}_3)\text{CO}_2\text{H}$ | 10 |
| $\text{CH}_3\text{CH}=\text{C}(\text{CH}_3)\text{CO}_2\text{H}$ | 38 |
| $\text{C}_6\text{H}_5\text{CH}=\text{CHCO}_2\text{H}$ | 100 |
| $\text{C}_6\text{H}_5\text{CH}=\text{C}(\text{CH}_3)\text{CO}_2\text{H}$ | 100 |

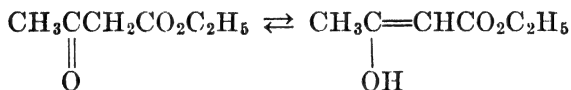
* Balance of product has OH on α -carbon atom.

In the discussion of α,β -unsaturated acids frequent references to and comparison with β,γ -unsaturated acids have been made.* The β,γ -unsaturated acids illustrate a very general tendency of β,γ -unsaturated systems to rearrange to conjugated α,β -unsaturated systems which are usually more stable.



β,γ -Unsaturated acids often show a tendency to form isomeric saturated lactones by intramolecular addition. Since this reaction is not reversible it will go to completion, and an α,β -acid may isomerize first to the β,γ -acid and then cyclize. γ,δ -Unsaturated acids form lactones and cyclic ketones.¹⁷⁹

When the unsaturation in the β,γ -position is a carbonyl group, keto-enol tautomerism occurs.



The factors affecting the stability of α,β - and β,γ -isomerides have been extensively investigated,¹⁸⁰ but, beyond noting that tautomerism is

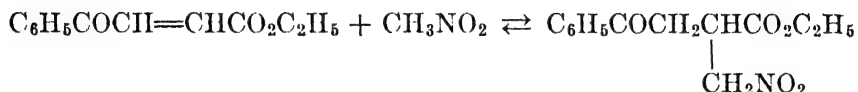
* The glutaconic acids, $\text{HO}_2\text{CCH}_2\text{CH}=\text{CHCO}_2\text{H}$, combine both α,β and β,γ unsaturation, and the chemistry of these acids and their derivatives has presented many problems of unusual interest. Though complex, the reactions of the glutaconic acids can be satisfactorily accounted for by the simultaneous occurrence of geometrical isomerism and 1,3-rearrangements, Kon and Nanji, *J. Chem. Soc.*, 2426 (1932); a detailed discussion of these reactions is beyond the scope of this chapter.

¹⁷⁹ Plattner and Pfau, *Helv. Chim. Acta*, **20**, 1474 (1937).

¹⁸⁰ Baker, "Tautomerism," Routledge and Sons, London (1934).

essentially an interconversion of α,β - and β,γ -unsaturated systems, it will not be discussed in this chapter.

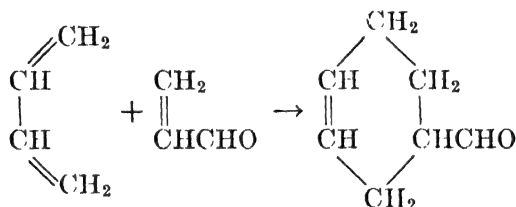
A comparison between the reactivities of two conjugated systems, in one of which an ethylenic linkage is conjugated with a carbonyl group while in the other the ethylenic linkage is conjugated with a carbalkoxy group, is possible using β -benzoylacrylic ester. With this compound HA reagents add to the conjugated system containing the carbonyl group.¹⁸¹



The Diene Synthesis

The diene synthesis consists of the 1,4-addition to a conjugated diene of an ethylenic compound in which the ethylenic linkage usually is, but need not be, part of a conjugated system. Isolated examples of the diene synthesis have been known for over fifty years,¹⁸² but the reaction was first recognized by Euler and Josephson¹⁸³ and has since been extensively developed by Diels and Alder.¹⁸⁴

A simple example of a diene synthesis is the addition of acrolein to butadiene.



It will be noticed that 1,4-addition has taken place, that the addend has not split, and that a cyclic compound has been formed. The more useful addends have been α,β -unsaturated compounds such as maleic anhydride, acrolein, acetylene dicarboxylic ester, and the quinones, but conjugated dienes can serve as addends (the dimerization of isoprene),¹⁸² as can ethylene itself and simple ethylenic compounds such as vinyl acetate and allyl chloride, in which the ethylenic linkage is activated by adjacency to a polar group.¹⁸⁵

Only 1,4-addition takes place in the diene synthesis even though the 1- and 6-positions are available.

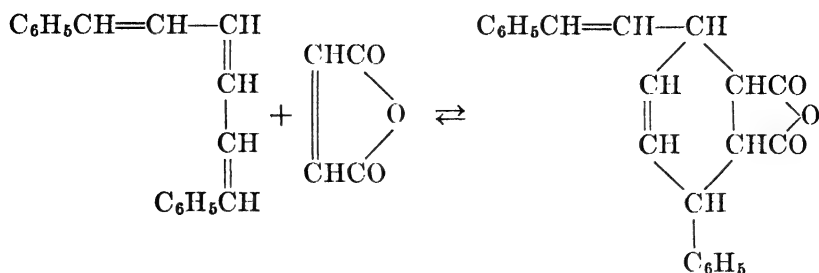
¹⁸¹ Kohler and Engelbrecht, *J. Am. Chem. Soc.*, **41**, 764 (1919).

¹⁸² Tilden, *J. Chem. Soc.*, **45**, 410 (1884).

¹⁸³ Euler and Josephson, *Ber.*, **53**, 822 (1920).

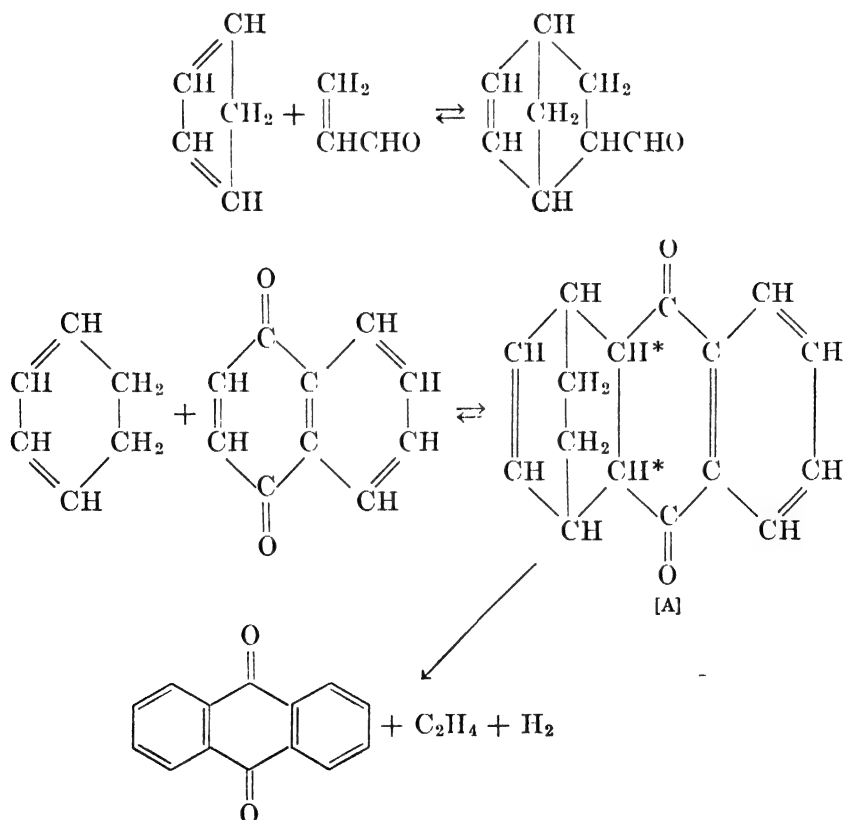
¹⁸⁴ Diels and Alder, *Ann.*, **460**, 98 (1928), and numerous later articles; also Adams and Gold, *J. Am. Chem. Soc.*, **62**, 56 (1940); Allen, Bell, Bell, and Van Allan, *ibid.*, 656.

¹⁸⁵ Alder and Rickert, *Ann.*, **543**, 1 (1939). Ketenes, however, do not enter into the diene synthesis; Smith, Agre, Leekley, and Prichard, *J. Am. Chem. Soc.*, **61**, 7 (1939); Joshel and Butz, *ibid.*, **63**, 3351 (1941).



Polyenes add one mole of maleic anhydride for each independent conjugated system; thus, diphenyldodecahexaene adds three moles of the anhydride.¹⁸⁶

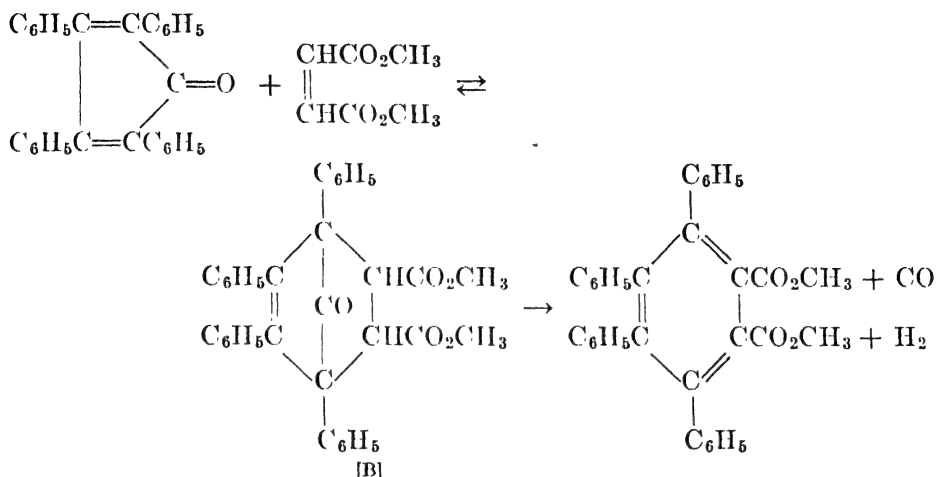
The diene synthesis is applicable to cyclic dienes, some furans, and coumalin.* When the diene is cyclic, bridged ring products result. Endoethylenic bridges, such as that in [A], are eliminated as ethylenic hydrocarbons on heating, and since the hydrogen atoms marked with asterisks are easily removed by oxidation, it is possible to convert the



¹⁸⁶ Kuhn and Wagner-Jauregg, *Ber.*, **63**, 2662 (1930).

* Heterocyclic nitrogen compounds react, but in a different manner.

addition products to aromatic compounds. When the structures of the aromatic compounds are known it is possible to work back to the structure of the diene. Carbonyl bridges, such as that in [B], are lost as carbon monoxide on heating, and the resulting dihydrobenzenes are easily dehydrogenated.¹⁸⁷



The diene synthesis always proceeds stereoselectively, to give polycyclic compounds with *cis* configurations at the ring junctions.¹⁸⁸

Diene additions make possible the synthesis of many otherwise inaccessible or difficultly accessible products, and they have been much used for proving structures and establishing the presence of conjugated systems. However, since it has been found that not all conjugated systems will enter into diene syntheses, the reaction is of diagnostic value only when it is positive.¹⁸⁹

Conjugation of an Ethylenic Linkage with a Nitrile or Nitro Group

In this brief section will be mentioned certain reactions of systems in which an ethylenic linkage is conjugated with some group other than those which have heretofore been discussed. The section is short as the purpose is less to describe new types of conjugation than to show that these new types exhibit the typical behavior of the conjugated systems which have already been considered.

The α,β -unsaturated nitriles undergo both 1,2- and 1,4-addition;

¹⁸⁷ Allen and Sheps, *Can. J. Research*, **11**, 171 (1934).

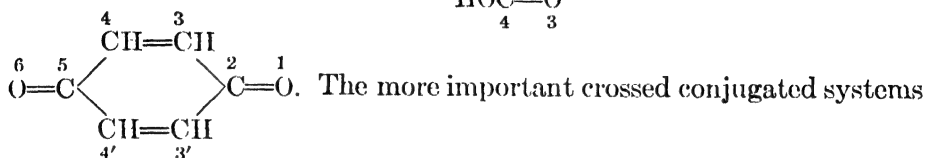
¹⁸⁸ Butz, Butz, and Gaddis, *J. Org. Chem.*, **5**, 171 (1940).

¹⁸⁹ Berchet and Carothers, *J. Am. Chem. Soc.*, **55**, 2004 (1933); Coffman and Carothers, *ibid.*, **55**, 2043 (1933).

Crossed Conjugated Systems

Three or more conjugated double bonds which are not arranged in a continuous chain form what is known as a crossed conjugated system.

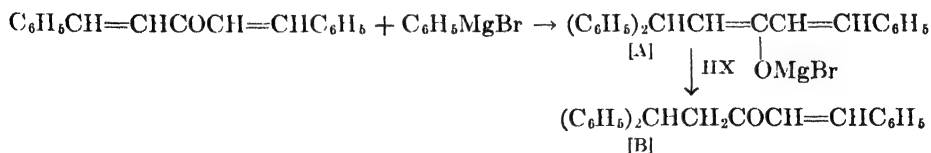
Examples are furnished by the pentadieneones, $\overset{6}{\text{C}}=\overset{5}{\text{C}}-\overset{3}{\text{C}}(\overset{2}{\text{C}}=\overset{1}{\text{C}})=\overset{4}{\text{O}}$, the branched-chained acids, $\overset{6}{\text{C}}=\overset{5}{\text{C}}-\overset{2}{\text{C}}(\overset{1}{\text{C}}=\overset{3}{\text{O}})=\overset{4}{\text{HOC}}=\overset{3}{\text{O}}$, and the *para*-quinones,



contain oxygen, and it will be noticed that they can be considered as being made up of two or more separate conjugated systems with one or more atoms in common.

The pentadieneones have been the subject of many investigations, as a result of which it is known that they show most of the characteristic reactions of the simpler α,β -unsaturated ketones. Halogen adds to the ethylenic linkages, and two moles of halogen may be added to pentadieneones. In general, however, it is more difficult to add the second mole than the first mole of a reagent to a pentadieneone, even though the product of addition of one mole still contains a conjugated system.

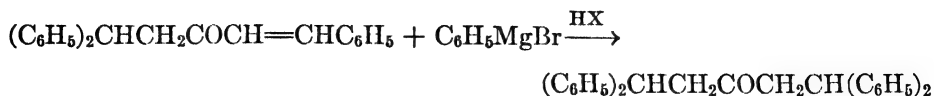
The Grignard reagent adds 1,4 to the conjugated system, $\text{C}=\text{C}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}$, in a pentadieneone,¹⁹³ even though an excess of the reagent is used, only one mole adds at a time.



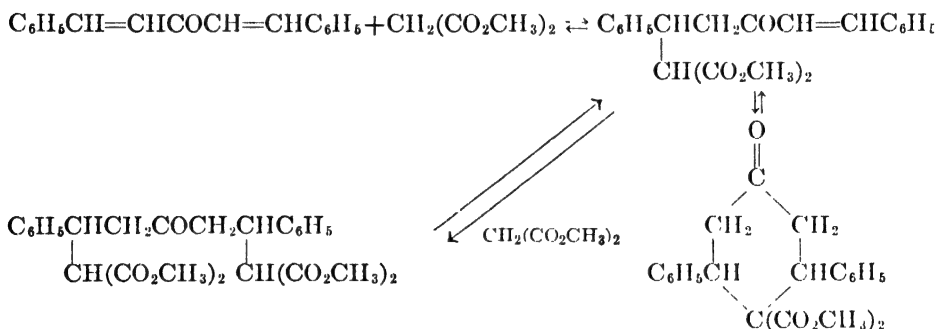
The reaction leading to the singly unsaturated ketone [B] affords striking evidence for 1,4-addition and against direct addition to the ethylenic linkage. A second mole of the Grignard reagent can be added but only after the conjugated system $\text{C}=\text{C}-\overset{\text{O}}{\text{C}}$ has been regenerated by

¹⁹³ Kohler, *Am. Chem. J.*, **37**, 369 (1907); **38**, 511 (1907); Woodward, Borchardt, and Fuson, *J. Am. Chem. Soc.*, **56**, 2103 (1934).

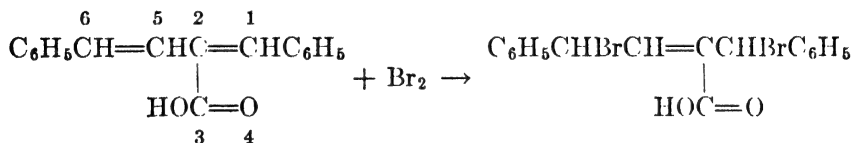
acidification of the magnesium derivative [A] and formation of the ketone [B].



The mode of addition to pentadieneones of substances having hydrogen atoms activated by adjacency to unsaturated groups is similar to the mode of addition of these same reagents to singly α,β -unsaturated ketones. The case of addition is affected by minor variations in the structures of the ketone or the addend, and the addition products often react further to furnish cyclic compounds. From dibenzalacetone and malonic ester, each of the three possible products has been isolated; the cyclic ester is the result of an intramolecular addition process which is perfectly analogous to the intermolecular addition of a substituted malonic ester to an α,β -unsaturated ketone.¹⁹⁴



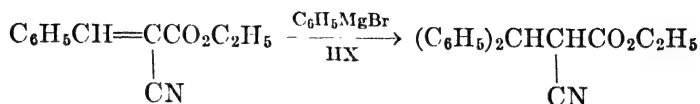
Dibenzalpropionic acid contains a crossed conjugated system which includes a carboxyl group.



Bromine adds mostly to the ends of the 1,2,5,6-system, but some 1,2-dibromide is formed. Hydrogen and compounds of the HA type, containing hydrogen activated by adjacency to an unsaturated group, add to the 1,2,3,4-system. These addends appear in the final products attached to the 1- and 2-carbon atoms; the addition, however, is doubtless conjugate followed by ketonization.

¹⁹⁴ Kohler and Helmkamp, *ibid.*, **46**, 1018 (1924); Kohler and Dewey, *ibid.*, **46**, 1267 (1924).

α -Cyanocinnamic ester contains a crossed conjugated system including a carbalkoxy and a cyano group. The addition of the Grignard reagent presumably takes place 1,4 to the system containing the cyano group, but the evidence for the location of the —MgBr group in the addition product is not conclusive.¹⁹⁵



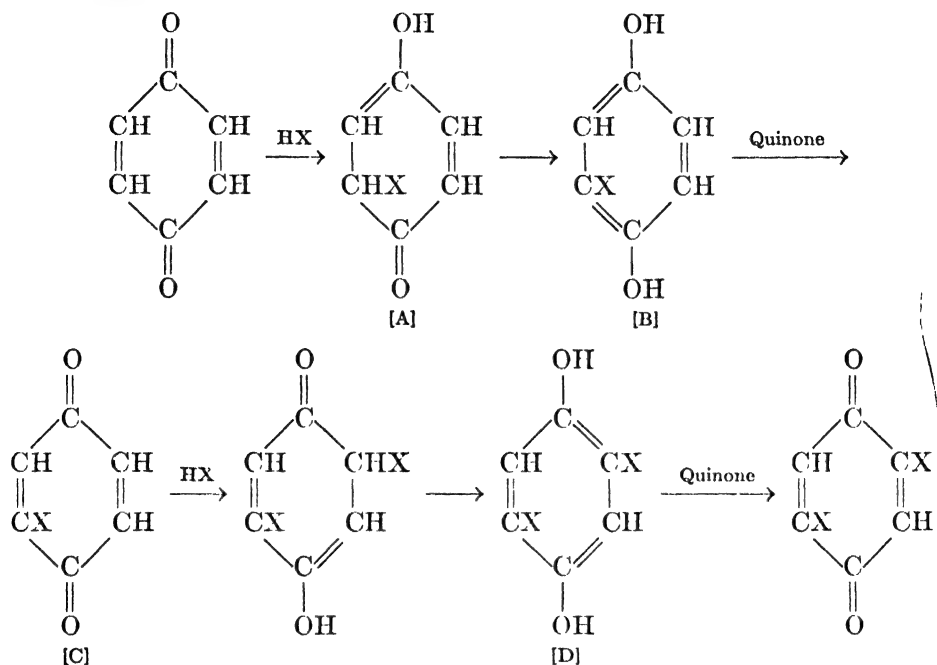
Quinones present a more complex picture than the substances heretofore considered since the presence of a second carbonyl group introduces additional complications. In many respects quinones resemble the unsaturated 1,4-diketones which are to be considered shortly. In the quinones there are two independent and four dependent conjugated systems of four atoms each, and two long conjugated systems of six atoms each, in addition to two carbonyl groups and two olefinic linkages that may function independently of each other. The isolation of all the compounds formed in an addition reaction involving a quinone is usually very difficult; not only is the reaction mixture composed of addition products but also there are substances resulting from oxidation and reduction reactions. Quinone adds bromine stepwise in the 3,4-positions, forming quinone di- and tetrabromides. Phenylazide, diazomethane, and the dienes also add in the 3,4-positions. On reduction hydroquinone results; the hydrogen is found on the oxygen atoms as a result of 1,6-addition. All quinones, regardless of the distance between the carbonyl groups, add hydrogen at the ends of the conjugated system. Substances having active hydrogen atoms (nitromethane, malonic ester, and the like) also add to quinones, but a complex mixture of products always results.

Perhaps the most interesting addition reactions of the quinones are those in which the addend is of the type HX . Hydrogen chloride yields mainly a chlorohydroquinone; aniline forms a mono- and a dianilinoquinone.¹⁹⁶ The formation of these products is readily accounted for by assuming that 1,4-addition first takes place; the intermediate [A] has an active hydrogen atom which undergoes enolization to give the substituted hydroquinone [B], which is then oxidized by a molecule of the original quinone to furnish a substituted quinone [C] while the oxidant is reduced to hydroquinone. Although a second molecule of HX could add in several ways, actually it adds in but one way to furnish [D].

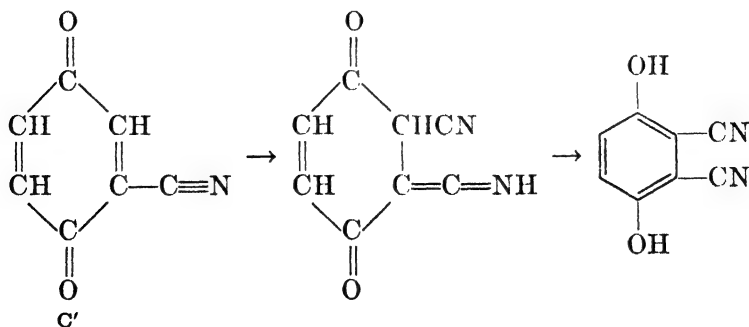
¹⁹⁵ Kohler and Reimer, *Am. Chem. J.*, **33**, 333 (1905).

¹⁹⁶ Suida and Suida, *Ann.*, **416**, 113 (1918).

The succeeding steps to the disubstituted quinone are a repetition of the preceding steps.



The addition of hydrogen cyanide is unique; two molecules of the reagent add, but in the resulting dicyanohydroquinone both cyano groups are on the same side of the benzene ring. The explanation is as follows: the first step resembles the scheme outlined above, a monocyanoquinone C' of type C resulting. This substance, however, contains an alternate conjugated system involving the nitrile group, to which hydrogen cyanide will add more readily than to the system $C=C-C=O$; ²¹⁷ rearrangement of the hydrogen atoms leads to the dicyanohydroquinone.¹⁹⁷

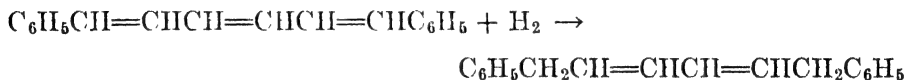


¹⁹⁷ Allen and Wilson, *J. Am. Chem. Soc.*, **63**, 1756 (1941).

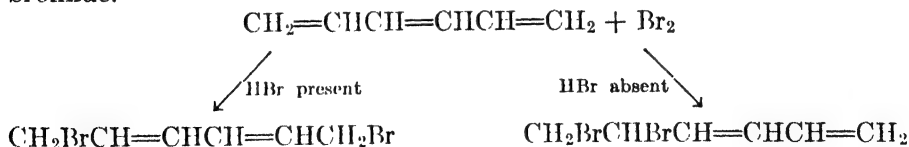
Long Conjugated Systems

The unsaturated compounds considered so far have contained, with the exception of the quinones, no more than two conjugated double bonds arranged in a continuous chain, and they have presented the possibilities of 1,2- and 1,4-addition. When three conjugated double bonds are arranged in a continuous chain the possibilities are more numerous: 1,2-addition at each double bond, 1,4-addition to either of the two conjugated systems, and 1,6-addition at the ends of the long conjugated system. With more than three conjugated double bonds arranged in a continuous chain the number of possible modes of addition is still greater, but such systems are not common and for the most part systems containing three conjugated double bonds only will be dealt with. Hydrogen, bromine, malonic ester, the Grignard reagent, and phosphorus pentachloride have been reported to undergo 1,*n*-addition, where *n* > 4, but this type of addition to the ends of long conjugated systems is common only with hydrogen.

The terminally phenylated dienes on reduction with metal combinations add but one mole of hydrogen, and the addition is always at the ends of the conjugated system.¹⁹⁸



On catalytic reduction with one mole of hydrogen these polyenes give mixtures of unattacked and completely reduced material; the reduction to phenylated paraffins is, of course, complete when sufficient hydrogen is used. A single example of 1,6-addition of halogen to a polyene has been reported; 1,3,5-hexatriene furnishes a 1,2-dibromide in the absence of hydrogen bromide and a 1,6-dibromide in the presence of hydrogen bromide.¹⁹⁹



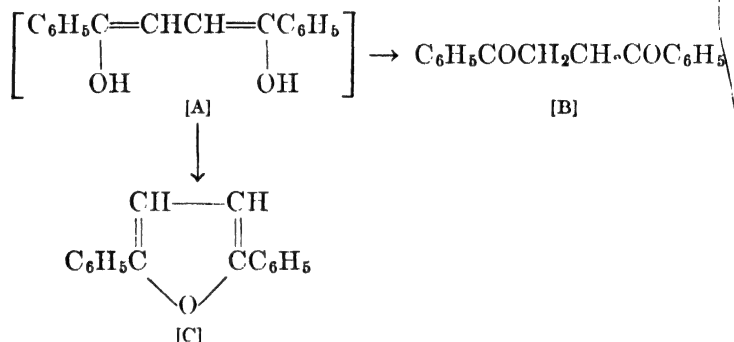
The other addition reactions of the polyenes are either 1,2 or 1,4.

Certain unsaturated 1,4-diketones furnish, on reduction, mixtures of saturated 1,4-diketones and furans. Since saturated 1,4-diketones are

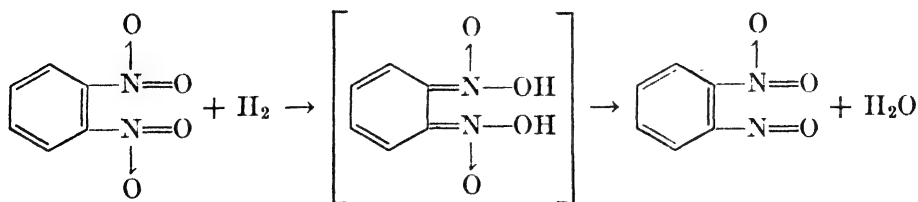
¹⁹⁸ Kuhn and Winterstein, *Helv. Chim. Acta*, **11**, 123 (1928). For a general discussion of the preparation, properties, and reactions of the phenylated polyenes compare *Helv. Chim. Acta*, **11**, 87-151 (1928).

¹⁹⁹ Farmer, Laroi, Switz, and Thorpe, *J. Chem. Soc.*, 2937 (1927).

known to furnish furans on dehydration, the formation of furans on reduction may proceed by way of the saturated ketones. It has been shown in several cases, however, that unsaturated 1,4-diketones can be reduced to yield, principally, furans under conditions such that no appreciable conversion of the saturated ketones to the furans takes place.²⁰⁰ This affords convincing evidence that the reduction of unsaturated 1,4-diketones proceeds through 1,6-addition and that the resulting dienol [A] may either rearrange to the saturated diketone [B] or eliminate water to form the furan [C], probably *via* a monoenol.²⁰¹



By analogy with the unsaturated 1,4-diketones, a 1,*n*-addition of hydrogen may be assumed to take place in the notably easy reduction of a number of long conjugated systems which terminate at both ends in oxygen; 1,6-addition in the reduction of maleic acid and its analogs, *o*-phthalic acid, the *para*-quinones, and many vat dyes; 1,8-addition in the reduction of terephthalaldehyde, muconic acid, and terephthalic acid; and even higher types of addition in the reduction of polynuclear quinones. In the examples just cited there is no direct evidence for the type of addition assumed, but the reduction of *ortho*- and *para*-dinitrobenzene to the nitrosodinitrobenzenes, under conditions such that *meta*-dinitrobenzene is not affected, does constitute evidence for 1,6 and 1,8-addition of hydrogen.²⁰²

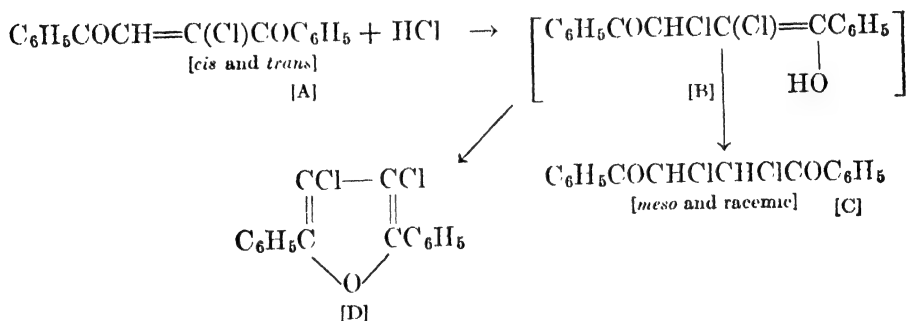


²⁰⁰ Lutz, *J. Am. Chem. Soc.*, **51**, 3008 (1929); Lutz and Reveley, *ibid.*, **61**, 1854 (1939)

²⁰¹ Lutz and Kibler, *ibid.*, **62**, 360 (1940).

²⁰² Meisenheimer, *Ber.*, **36**, 4174 (1903).

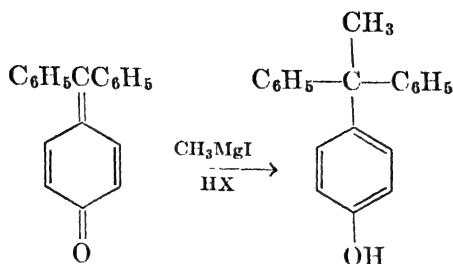
Returning again to the unsaturated 1,4-diketones, it is to be noted that the addition of reagents other than hydrogen is 1,2 or 1,4, but never 1,6. Halogen, as usual, adds 1,2 to the ethylenic linkage. Halogen acids add 1,4 to the system $C=C-C=O$, and the addition products serve to establish the mechanism as 1,4-addition with hydrogen entering the molecule at an oxygen atom. Both *cis*- and *trans*-dibenzoylchloroethylenes [A] add hydrogen chloride in chloroform or ether to give mixtures of *meso* and racemic dibenzoylchloroethanes [C]. The ratio in which the chloroethanes are formed is dependent on the conditions under which the addition is carried out and not on the configuration of the starting materials. Both the *meso* and racemic chloroethanes are stable under the conditions obtaining in the addition reactions so that there is no isomerization due to the reagents. These apparent stereochemical inconsistencies can be interpreted on the assumption that 1,4-addition of hydrogen chloride takes place to form the enol [B], for in this process the stereoisomerism about the ethylenic double bond in the starting material is destroyed. The enol can then ketonize to form the chloroethanes, and the ratio in which the chloroethanes are formed will be dependent on the conditions under which ketonization takes place and independent of the configuration of the chloroethylene used. The enol [B] may also lose a molecule of water to form the furan [D]. When the addition of hydrogen chloride is carried out in alcohol the furan [D] is obtained, and this, since the chloroethanes [C] are not converted to the furan [D] under these conditions, is additional evidence for 1,4-addition.²⁰³



The addition of the Grignard reagent to unsaturated 1,4-diketones furnishes 1,4- and sometimes 1,2-addition products. Thus, dibenzoyl-ethylene and phenylmagnesium bromide give desylacetophenone,²⁰⁴ and phenyldibenzoyl-ethylene with the same reagent furnishes bidesyl

²⁰³ Lutz and Wilder, *J. Am. Chem. Soc.*, **56**, 1193 (1934).

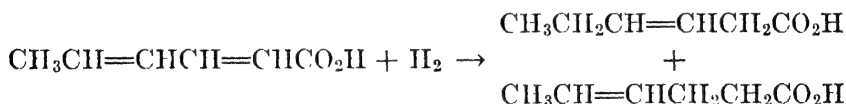
²⁰⁴ Lutz and Tyson, *ibid.*, **56**, 1341 (1934).



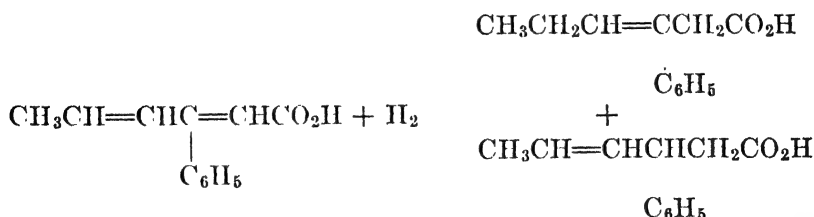
All other attempts to secure 1,6-addition of the Grignard reagent have been unsuccessful, and earlier claims of 1,6-addition have not been substantiated.²⁰⁹

A relatively wide variety of doubly unsaturated acids and esters has been available, and from the study of their addition reactions many interesting results have been obtained. The nature of the products of partial catalytic reduction of these acids and esters is still controversial. For certain reactions dihydro reduction products have been described²¹⁰ but not always confirmed.²¹¹ Differences in experimental conditions and in the nature of the catalyst may account for the divergent results so far reported. At one time it was believed that the addition of but one mole of hydrogen to a doubly unsaturated acid or ester always gave mixtures of unattacked material and completely reduced products.²¹²

In contrast with catalytic reduction, sodium amalgam usually gives a mixture of dihydro derivatives which may be accounted for by 1,4- and 1,6-addition. Sorbic acid furnishes two isomeric dihydro derivatives whose structures have been established by synthesis.²¹³



β -Phenylsorbic acid gives a mixture of analogous dihydro products.²¹⁴



²¹⁰ Muskat and Knapp, *Ber.*, **64**, 779 (1931); Farmer and Galley, *J. Chem. Soc.*, 430 (1932); Farmer and Hughes, *ibid.*, 304, 1929 (1934); Farmer and Hughes, *J. Soc. Chem. Ind.*, **53**, 131 (1934).

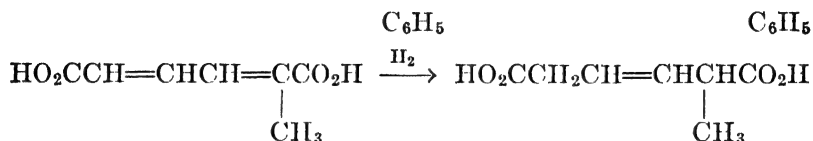
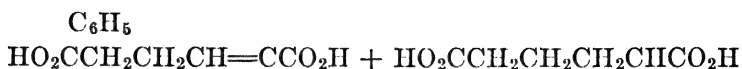
²¹¹ Ingold and Shah, *J. Chem. Soc.*, 885 (1933).

²¹² Hückel, "Theoretische Grundlagen der organischen Chemie," Akad. Verlags. Leipzig (1931), Vol. I, p. 340.

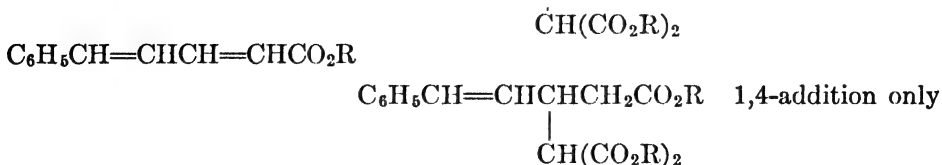
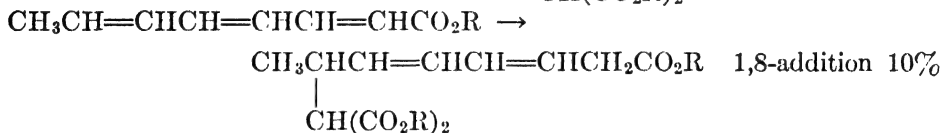
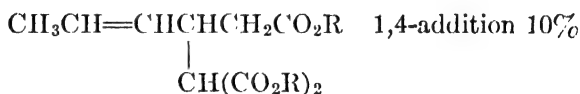
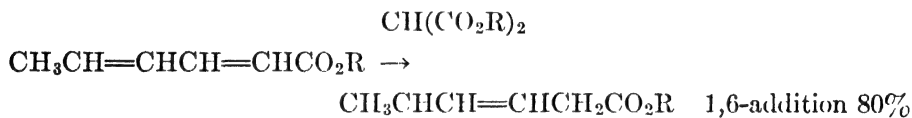
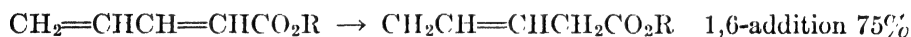
²¹³ Burton and Ingold, *J. Chem. Soc.*, 2022 (1929).

²¹⁴ Kuhn and Hoffer, *Ber.*, **66**, 1263 (1933).

α -Phenylmuconic acid furnishes 23 per cent of the 3,4-dihydro product, the balance of the material undergoing complete reduction, and α -methylmuconic acid gives 80 per cent of the 1,4-dihydro acid.²¹⁵



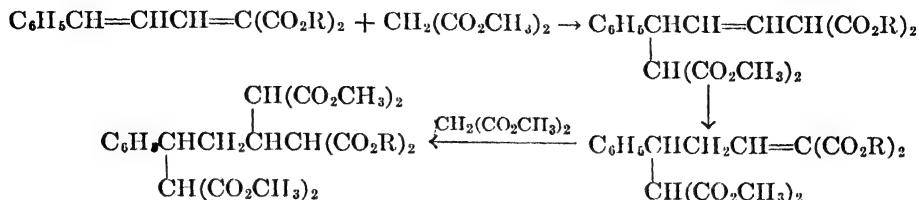
A number of esters of the malonic type have been added to the doubly unsaturated esters. The mode of addition varies markedly using a single addend and a series of unsaturated esters. The yields reported are none too accurate because of experimental difficulties, and in some cases not all the starting material can be accounted for. The results using malonic ester are shown by the following reactions.*



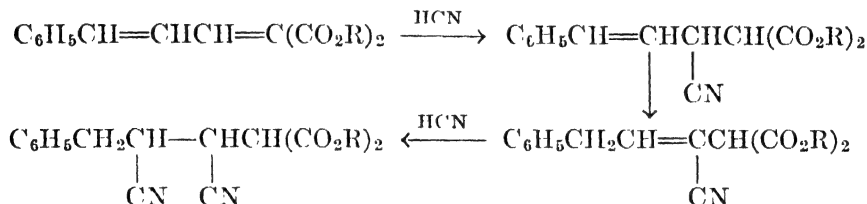
²¹⁵ Kuhn and Michel, *Ber.*, **71**, 1119 (1938).

* A summary of earlier work together with new experimental data on 1,6-addition is given by Kohler and Butler, *J. Am. Chem. Soc.*, **48**, 1036 (1926). Compare (a) Farmer and Healy, *J. Chem. Soc.*, 1060 (1927); (b) Farmer and Mehta, *ibid.*, 1610 (1930); (c) Farmer and Martin, *ibid.*, 960 (1933).

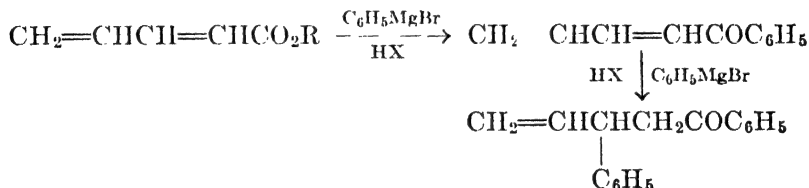
Cinnamalmalonic ester adds two moles of malonic ester.²¹⁶ This can be accounted for by 1,6-addition of one mole of the addend followed by a shift of one hydrogen atom to furnish a new conjugated system which adds a second molecule of malonic ester in the 1,4-positions.



Two moles of hydrogen cyanide can also be added to cinnamalmalonic ester, and in this reaction the primary 1,4-addition product can be isolated.²¹⁷ The addition of the second mole of hydrogen cyanide is 1,4 and involves the cyano group.



The addition of the Grignard reagent to the doubly unsaturated esters never furnishes 1,6-addition products. The most favorable case is β -vinylacrylic ester, and this substance is first converted to a ketone which then undergoes only 1,4-addition.



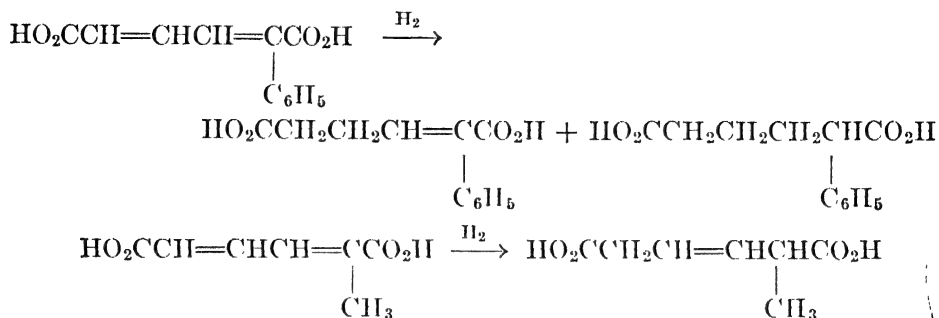
The reluctance of the Grignard reagent to undergo 1,6-addition is characteristic of most addends, for, with the exception of esters and hydrogen, the great majority of reagents which undergo 1,4-addition to α,β -unsaturated esters and carbonyl compounds undergo only 1,4-addition to the analogous doubly unsaturated systems where 1,6-addition is a possibility.²¹⁸ In contrast with 1,4-addition, which is one of the commonest modes of reaction of conjugated systems, 1,6-addition is unusual.

²¹⁶ Meerwein, *Ann.*, **360**, 325 (1908).

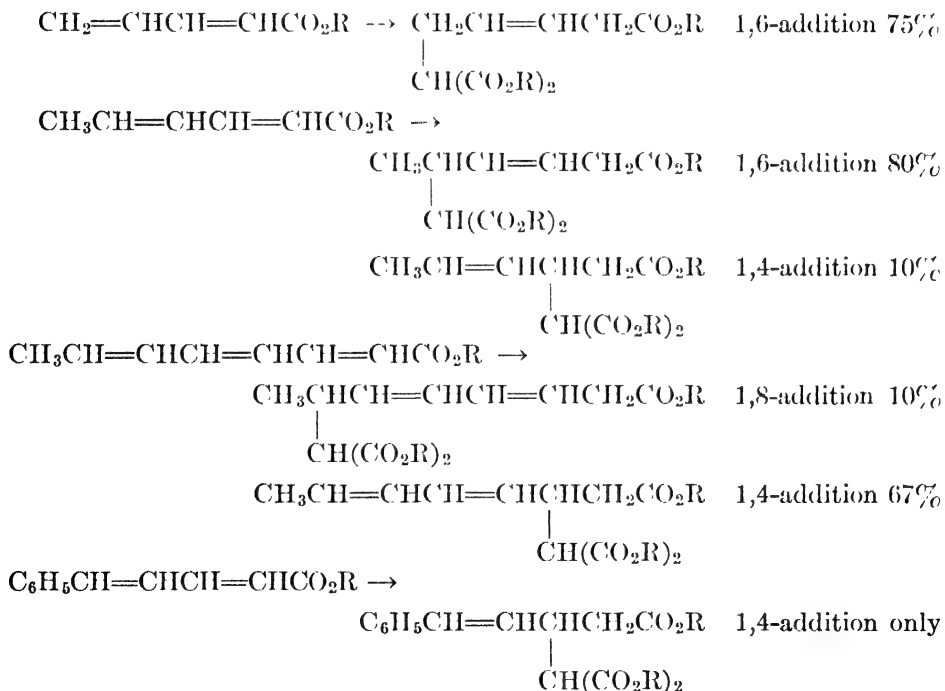
²¹⁷ Duff and Ingold, *J. Chem. Soc.*, 87 (1934).

²¹⁸ Ingold, Pritchard, and Smith, *ibid.*, 81 (1934); Kohler and Butler, *J. Am. Chem. Soc.*, **48**, 1036 (1926).

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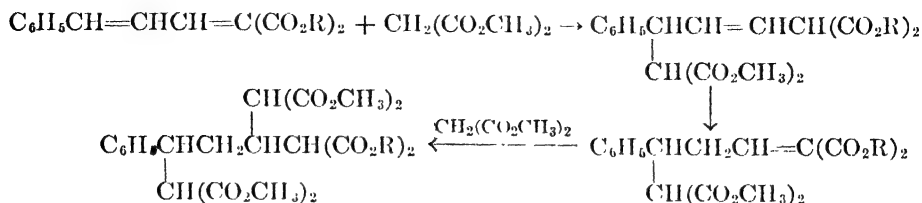
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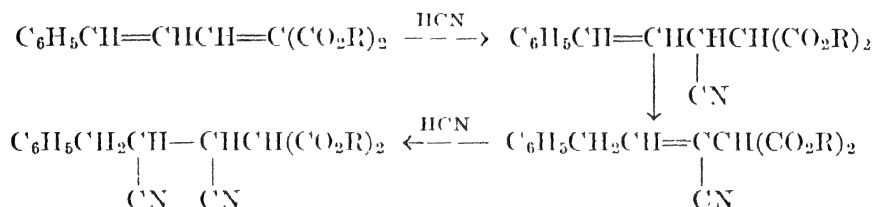
²¹⁵ Kuhn and Michel, *Ber.*, **71**, 1119 (1938).

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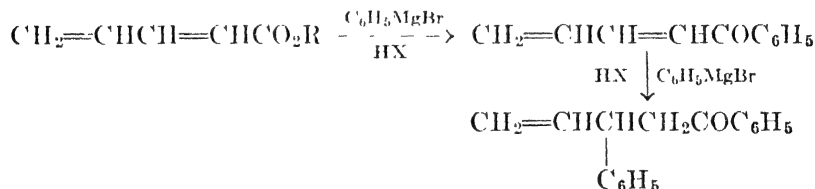
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²¹⁶ Meerwein, *Ann.*, **360**, 325 (1908).

²¹⁷ Duff and Ingold, *J. Chem. Soc.*, 87 (1934).

²¹⁸ Ingold, Pritchard, and Smith, *ibid.*, 81 (1934); Kohler and Butler, *J. Am. Chem. Soc.*, **48**, 1036 (1926).

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CHAPTER 8

SYNTHETIC POLYMERS

C. S. MARVEL AND E. C. HORNING*

University of Illinois

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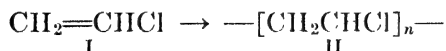
INTRODUCTION

The term polymer was introduced into organic chemistry by Berzelius¹ more than a century ago to designate the more complex of two substances having identical composition but differing in molecular weight. There was no idea of any other relation between the two substances in this definition. In later years, the term polymerization came to be applied to the process of self-addition of unsaturated compounds to give products which appear to have the same composition but multiple molecular weight. The terms polymer and polymerization are now used almost exclusively in connection with very-high-molecular-weight compounds.

The careful study of polymers or macromolecules which has been going on for about the last twenty years constitutes one of the important developments of modern organic chemistry.

It is now known that few, if any, addition polymers (macromolecules) have exactly the composition of the monomers from which they are formed. The process of self-addition is usually interrupted by the addition of one or more foreign molecules giving terminal groups which are very different in composition from the monomer. The classical work of Staudinger and L  thy² on the polyoxymethylenes illustrates this possibility. When formaldehyde polymerizes, the reaction may be interrupted by the addition of water to yield $\text{HO}[\text{CH}_2\text{O}]_n\text{H}$, methyl alcohol to give $\text{CH}_3\text{O}[\text{CH}_2\text{O}]_n\text{H}$, etc. Carothers' work on polyesters and polyamides has brought these polymer-forming reactions to the attention of chemists. These polymers differ markedly in composition from the reactants which produce them because of the loss of some small molecule such as water during their formation, yet such reactions seem best described as polymerization processes.³

Polymerization reactions are intermolecular combinations that are functionally capable of proceeding indefinitely and thus may theoretically lead to molecules of unlimited size. Polymers can be classified as addition polymers and condensation polymers. The addition polymers are formed by intermolecular reactions of the monomeric units without the elimination of any atoms or groups. Thus vinyl chloride (I) combines with itself to produce polyvinyl chloride (II). In writing the

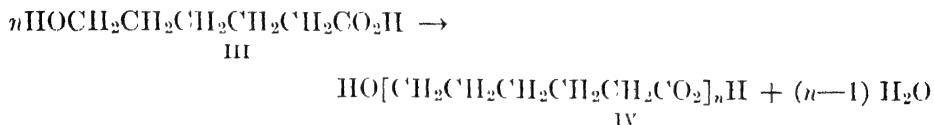


¹ Berzelius, *Jahresber.*, **12**, 64 (1833).

² Staudinger and L  thy, *Helv. Chim. Acta*, **8**, 41 (1925).

³ Carothers, *J. Am. Chem. Soc.*, **51**, 2548 (1929).

polymer as in structure II, no indication is given as to what is at the ends of this polymeric chain. Condensation polymers are produced by reactions which involve elimination of some simple molecule between two functional groups; such reactions are esterification, anhydride formation, amide formation, aldol condensation, etc. The self-esterification of ϵ -hydroxycaproic acid (III) serves to illustrate this type. The reaction between a dibasic acid and a glycol runs similarly. There are also cases which seem to be hybrids between these two fundamental types (see p. 768).



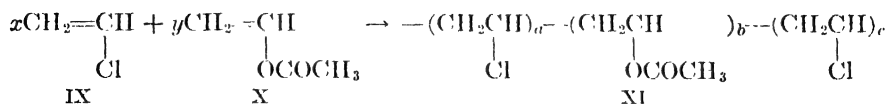
Reactions of the types indicated lead to high-molecular-weight chains or *linear* molecules which have a characteristic *recurring unit*. The character of this unit is a factor of great importance in determining the nature of the polymer. The physical properties of linear polymers are related to their molecular size and to the nature of the recurring units. It is at once rather evident that in a synthetic linear polymer it is not likely that each individual polymer chain will be exactly the same length as every other chain. Hence, a synthetic polymer will not be strictly a chemical individual from this point of view. The natural polymers do not have the wide variations in average chain length which are characteristic of the synthetic polymers.

There are many possible polyfunctional reactions, and some of these lead to products which are not linear. The well-known esterification of glycerol by phthalic anhydride to produce a polyester (V) is an example of the formation of a *three-dimensional polymer*.

Such a three-dimensional polymer as this is always insoluble, infusible, and generally intractable. There are all gradations between the true linear polymer and the three-dimensional type. The *cross-linked polymers* have properties falling between the two extreme cases. They are usually less soluble than the linear esters but may swell with solvents, whereas the true three-dimensional polymer is usually entirely unaffected by solvents.

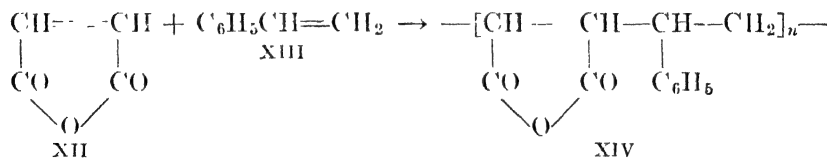
Self-addition reactions of such compounds as the 1,3-dienes may lead to complex cross-linked polymers. The rubber molecule produced in the living plant (VII) is apparently made up of isoprene units (VI) joined in the 1,4-positions.

are known as *copolymers*. The best-known examples of this type of polymer are the various "Vinylite" resins (XI) made from vinyl chloride (IX) and vinyl acetate (X). The term copolymer has not been com-



monly applied to the condensation polymers, but it might be used for such a substance as a polyester made from two or more dibasic acids with one or two polyhydric alcohols, etc.

Another type of polymerization reaction that is sometimes encountered is the copolymerization of two unsaturated molecules, one of which does not normally undergo addition polymerization. Thus maleic anhydride (XII), which alone does not polymerize, will copolymerize with styrene (XIII) to give a linear polymer (XIV). Such a polymer has been called a *heteropolymer*.⁴



In condensation polymers the *end groups* are the functional groups of the original reacting molecules. Thus, if a hydroxy acid is converted to a polyester, the polymer will have a hydroxyl group at one end of the chain and a carboxyl group at the other. If two reacting molecules such as a glycol and a dibasic acid are used, the end groups may be hydroxyl and carboxyl, two hydroxyls, or two carboxyls, depending on the ratios of the reactants.

In addition polymers the end groups are less well known. They may be parts of the catalyst used to initiate the reaction (p. 775); they may result from a disproportion of reacting chains; they may come from a reaction between growing chains and impurities in the monomer or solvents used for the reaction. In the past the end groups have usually been written as hydrogen and a double bond; for the present, however, it is probably wisest not to attempt to indicate end groups on most vinyl polymers.

It should be realized that not all reactions between bifunctional molecules will produce useful polymers. To give products with a molecular weight high enough to make the polymer useful, the reaction of formation must be one which proceeds smoothly and in excellent

⁴ Wagner-Jauregg, *Ber.*, **63**, 3213 (1930).

yields. In general, any reaction which gives yields of less than 90 per cent between simple molecules can be overlooked as a useful polymer-forming reaction. To obtain macromolecules, clean-cut reactions with few possibilities for side reactions are essential.

The older literature is full of references to tarry side products and insoluble residues when bifunctional or polyfunctional reactions were carried out. In the early days of the scientific development of the polymer field, the orthodox organic chemist called the polymer chemist a student of "gunks" and indicated that the purity of his products was far less than that demanded in ordinary synthetic work. Actually nothing can be farther from the truth. To obtain useful high-molecular-weight products it is essential that starting materials have an extremely high degree of purity, often far above that of so-called analytical purity.

There is another type of rather large molecular aggregate which is sometimes described as a polymer. Certain organic molecules such as ethyl alcohol and acetamide which contain active hydrogen as hydroxyl or amido hydrogens and donor atoms such as oxygen and nitrogen are rather firmly joined together by hydrogen bonds. These products are really polymeric in nature, but they differ markedly in stability from the polymers in which the units are held together by covalences. The polymers held together by hydrogen bridges usually have the chemical reactions of the monomer although the physical properties (boiling point, melting point, solubility, etc.) are out of line with those predicted for the monomer. These may be called *association polymers*.

CONDENSATION POLYMERIZATION

Condensation polymers may be produced from a great variety of polyfunctional compounds. Generally speaking, any reaction between simple functional groups may be adapted to polymer formation. There is no essential difference between a condensation reaction which produces a polymer and a similar reaction which produces low-molecular-weight molecules. However, to obtain satisfactory polymeric products, the reactants must be pure, they must be used in the proper ratios, and the reactions must take place almost quantitatively.

In the following pages the synthetic polyesters, polyamides, polysulfides, urea-formaldehyde condensation products, phenol-formaldehyde condensation products, polyethers, polyacetals, polyanhydrides, and a few other miscellaneous condensation polymers will be discussed

Polyesters

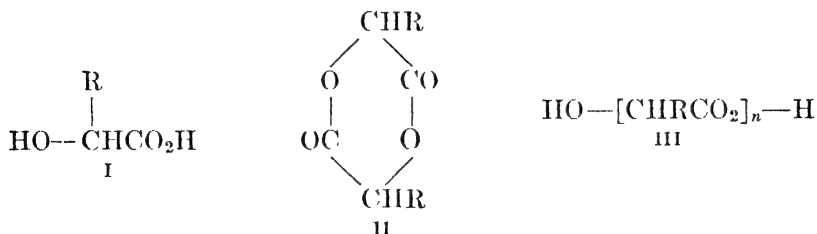
The polyesters first became technically important as alkyd resins; later they were studied from the theoretical standpoint. The discussion of these esters will not follow their historical development.

Hydroxy acids will undergo self-esterification to produce the simplest type of polyesters, but glycols and dibasic acids, or polyglycols and polybasic acids, give the same type of reaction and produce correspondingly more complex products.

With bifunctional molecules, ring formation will compete with linear polymer formation. Carothers³ has pointed out that under the usual reaction conditions a five- or six-membered ring will usually form whenever that is possible. In all other cases polymer formation is the favored reaction. However, special conditions may alter the course of a reaction. Thus Ruggli⁵ has demonstrated the value of the high-dilution principle for producing large rings. The application of these principles can best be demonstrated by a discussion of particular cases. Structural features in the reacting units may also affect the balance between ring formation and polymer formation.

Polyesters from Hydroxy Acids. When any hydroxy acid $\text{HO}(\text{CH}_2)_n(\text{CO}_2\text{H})$ (except a β -hydroxy acid) is heated with or without a catalyst, self-esterification proceeds. The nature of the product depends on the distance between the hydroxyl group and the carboxyl group.

In the case of α -hydroxy acids (I), self-esterification usually produces a lactide (II) although linear esters (III) are known. Glycolic acid (I, $\text{R} = \text{H}$) on gentle heating is said to give glycolide (II, $\text{R} = \text{H}$). The cyclic ester on heating with a trace of zinc chloride is converted to a linear polyester (III, $\text{R} = \text{H}$). Distillation under reduced pressure



causes the polyester to revert to the cyclic ester.⁶ Lactic acid (I, $\text{R} = \text{CH}_3$) gives lactide (II, $\text{R} = \text{CH}_3$) at 150° ,⁷ but under other

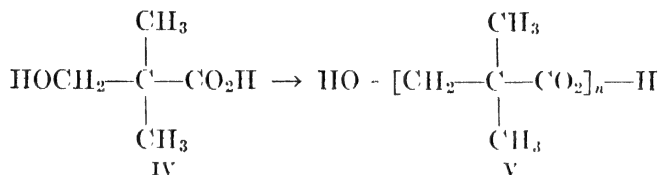
⁵ Ruggli, *Ann.*, **392**, 92 (1912).

⁶ Bischoff and Walden, *Ber.*, **26**, 262 (1893); *Ann.*, **279**, 45 (1894).

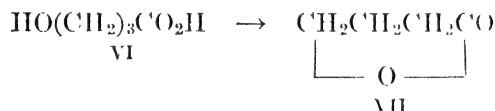
⁷ Bischoff and Walden, *Ann.*, **279**, 71 (1894).

conditions Dietzel and Krug⁸ have obtained a linear polylactic acid. Lactide heated at 250–275° for two hours is converted into a linear polymer with a molecular weight of about 3000.⁹ If a catalyst such as potassium carbonate is present this transformation occurs at about 140–150°.

β -Hydroxy acids usually lose water to give α,β -unsaturated acids so readily that self-esterification does not occur. If, however, substitution prevents dehydration, heat converts β -hydroxy acids to linear polymers; thus hydroxypivalic acid (IV) gives a product (V) with a molecular weight of about 600 (n = about 6),¹⁰ but considerable decomposition of the monomer into formaldehyde and isobutyric acid accompanies this reaction.

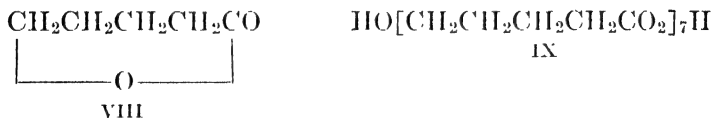


γ -Hydroxy acids, such as γ -hydroxybutyric acid (VI), readily give the γ -lactones which are very stable. γ -Butyrolactone (VII) has been



heated to 80° with and without catalysts for as long as twelve months without the formation of a detectable amount of polymer.⁹

δ -Hydroxy acids also readily give δ -lactones, but these six-membered lactones often change spontaneously into the linear polyesters. Fichter and Beisswenger¹¹ observed that δ -valerolactone (VIII) gradually becomes thicker and more viscous on standing and finally yields a solid polymer (IX) with about seven recurring units. It seems probable that



some trace of water or acid is necessary for this reaction to take place. Carothers, Dorrough, and Van Natta⁹ found that the molecular weight of the polymer varied with the method of preparation and obtained

⁸ Dietzel and Krug, *Ber.*, **58**, 1307 (1925).

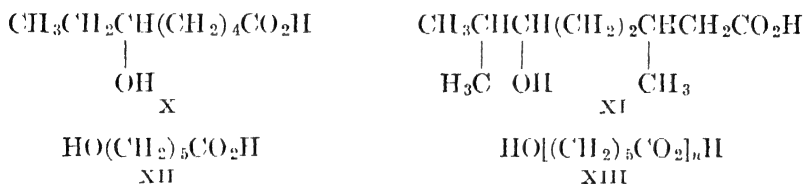
⁹ Carothers, Dorrough, and Van Natta, *J. Am. Chem. Soc.*, **54**, 761 (1932).

¹⁰ Blaise and Maucilly, *Bull. soc. chim.*, [3] **31**, 308 (1904).

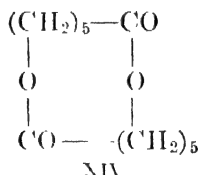
¹¹ Fichter and Beisswenger, *Ber.*, **36**, 1200 (1903).

values from 1060 to 2240 (10 to 22 monomer units). Hollo¹² found that substitution on the α -carbon atom decreases the ease of hydrolysis of δ -lactones and also the ease with which they polymerize.

When the hydroxyl is in the *epsilon* position, lactone formation is not the usual behavior of a straight-chain hydroxy acid, but substitution in the carbon chain may have a favorable influence on ring formation and promote lactonization. Thus, 6-hydroxyoctanoic acid (X)¹³ and 3,7-



dimethyl-6-hydroxyoctanoic acid (XI)¹⁴ give lactones when heated. 6-Hydroxycaproic acid (XII) gives a lactone at 150–210°¹⁵ but tends to polymerize at 150° to give a linear ester containing about 35 monomeric units (XIII). Once the linear ester is produced there is very little tendency for it to depolymerize to give the cyclic monomeric lactone, although a fourteen-membered dilactone (XIV) is produced in small amounts.



When the hydroxyl is farther from the carboxyl than the 6-position, only linear products are obtained on heating the acid. Chuit and Haussner¹⁶ have prepared the series of hydroxy acids (XV) with n having values of 7 to 20 and converted them to the corresponding linear polyesters (XVI).



Sabiniic acid (12-hydroxydodecanoic acid) and juniperic acid (16-hydroxyhexadecanoic acid) have been isolated from conifers, and it has been suggested that they exist as linear polyesters in the natural state.¹⁷

¹² Hollo, *Ber.*, **61**, 895 (1928).

¹³ Blaise and Koehler, *Compt. rend.*, **148**, 1772 (1909).

¹⁴ Baeyer and Seuffert, *Ber.*, **32**, 3619 (1899).

¹⁵ Van Natta, Hill, and Carothers, *J. Am. Chem. Soc.*, **56**, 455 (1934); **58**, 183 (1936).

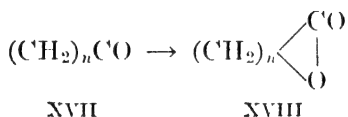
¹⁶ Chuit and Haussner, *Helv. Chim. Acta*, **12**, 463 (1929).

¹⁷ Bougault and Bourdier, *Compt. rend.*, **147**, 1311 (1908); *J. pharm. chim.*, [6] **29**, 561 (1909); [6] **30**, 10 (1909); Bougault, *ibid.*, [7] **1**, 425 (1910); [7] **3**, 101 (1911); *Compt. rend.* **150**, 874 (1910); Bougault and Cattelain, *ibid.*, **186**, 1746 (1928).

Lycan and Adams¹⁸ prepared a series of hydroxy acids of type XV in which n was 8, 9, 10, 11, and 12. 10-Hydroxydecanoic acid polymerized with heat to give a polymer (XVI) of a molecular weight of approximately 9000. Self-esterification of the hydroxy acid by heating a benzene solution containing a little *p*-toluenesulfonic acid gave a polymer having a lower molecular weight (about 2500). These polyesters were shown to contain hydroxyl and carboxyl end groups. They gave sharp x-ray diffraction patterns.

Large lactone rings can be prepared by self-esterification of the hydroxy acids under conditions of high dilution. Ruggli⁵ first suggested that a reaction which normally led to polymeric products could be made to yield a cyclic product if the distance between the different molecules were made greater than the distance between the two ends of one molecule. This dilution effect cuts down intermolecular reaction. By adopting this technique, high yields of such lactones as those of ω -hydroxypentadecanoic acid have been obtained.¹⁹ Once these large cyclic lactones are obtained, they show little tendency to rearrange to the linear polymers unless heated with catalysts.^{9, 27}

Ruzicka and Stoll²⁰ have prepared the simple lactones (XVIII) containing fourteen to eighteen members in the ring by oxidation of the corresponding cyclic ketones (XVII) with Caro's acid. This reaction



evidently does not involve converting the cyclic ketone to a linear intermediate.

In general the linear polyesters which have been prepared from hydroxy acids are white powders, soluble in many hot organic solvents. Their molecular weight varies, but it never approaches the values observed for the higher polystyrenes. The reasons for the comparatively low molecular weight of the product may be found in the relation between the nature of the polymerization and the experimental conditions employed.²¹ The macromolecule may be built up through successive couplings resulting finally in long chains. The reaction is reversible, however, and a large number of factors are involved. The equilibrium may be displaced by the removal of the water as it is formed in

¹⁸ Lycan and Adams, *J. Am. Chem. Soc.*, **51**, 625, 3450 (1929).

¹⁹ Stoll and Rouvé, *Helv. Chim. Acta*, **17**, 1283 (1934). Stoll, Rouvé, and Stoll-Comte *ibid.*, **17**, 1289 (1934).

²⁰ Ruzicka and Stoll, *ibid.*, **11**, 1159 (1928).

²¹ Carothers and Hill, *J. Am. Chem. Soc.*, **54**, 1559 (1932).

the reaction; this would tend to direct the reaction to completion. Formal completion of the process would obtain when all the small molecules were combined into a single molecule. Ester interchange may also be effective in producing large molecules. This has been demonstrated in the transformation of di-(β -hydroxyethyl) succinate into a linear polyester under the influence of heat.

Factors which may influence the upper limit of molecular size are the possibility of ring formation and accidental mutilation of the terminal groups. Experimental evidence seems to show that ring formation does not occur to a significant extent except under certain well-defined conditions, although in certain cases dimeric products of a cyclic nature have been observed.^{3, 9, 22} The mutilation of end groups, as for example loss of carbon dioxide from a carboxyl group, does not occur except under extreme thermal conditions, and even then coupling might still proceed through a process of ester interchange. In many cases small traces of impurities in the acids may be the chief cause of stopping the reaction.

The failure of the reaction to proceed to the formation of very large molecules is ascribed by Carothers and Hill²¹ to a combination of circumstances. The concentration of reactive groups becomes necessarily very low as the reaction proceeds, and the viscosity of the esters increases continuously. This operates to decrease the mobility of the molecules and decreases also the rate of diffusion of volatile products, such as water, to the surface. Also, macromolecules in general show a pronounced tendency to retain dissolved or adsorbed liquids. This may be due to their exaggerated molecular cohesions.²³ It, therefore, would be reasonable to expect that a more effective means of removing volatile products would lead to higher-molecular-weight products than those hitherto observed. The use of a molecular still²⁴ has partially fulfilled these conditions, and superpolyesters have been obtained.^{21, 22} The same results have been achieved in a lesser degree by prolonged heating of the lower polyesters in thin layers in a nitrogen stream, or by bubbling nitrogen through the molten esters.

The linear polyesters of low molecular weight (usually in the neighborhood of 3000) are microcrystalline powders which dissolve readily in chloroform to yield mobile solutions, and have already been described. The superpolyesters (those of molecular weight 12,000–25,000) are harder and much tougher when prepared in a massive state. In cold chloroform they dissolve very slowly with a pronounced swelling,

²² Carothers and Van Natta, *ibid.*, **55**, 4714 (1933).

²³ Dunkel, *Z. physik. Chem.*, **A138**, 42 (1928).

²⁴ Carothers and Hill, *J. Am. Chem. Soc.*, **54**, 1557 (1932).

and their solutions are quite viscous. Their structure is undoubtedly that of a long polymeric chain.

The polyesters from ω -hydroxydecanoic acid, $\text{HO}(\text{CH}_2)_9\text{COOH}$, have been examined carefully.²² Molecular weights have been observed varying from 780 to 25,200 depending on the conditions of polymerization, the higher values resulting from the most drastic treatment. The melting points varied from 66–67° to 75–80°. The molecular weights were obtained by titration with standard alcoholic potash of the polyesters dissolved in a chloroform-alcohol mixture. Phenolphthalein was used as the indicator. The lower values were checked by a boiling-point method and the highest by the use of the ultracentrifuge. The masses resulting from crystallization of the molten polyesters were opaque solids. The lower members were waxy and brittle; the higher members were harder and so horny and tough that they could scarcely be fractured.

The polyesters of molecular weight less than 10,000 dissolved rapidly and completely in cold chloroform or benzene and in hot acetone, ethyl acetate, and acetic acid. They were practically insoluble in hot alcohol, ligroin, or water. The highest members showed a diminished solubility. At about 110° the first member of the series was a highly viscous liquid while the highest member was a transparent resin.

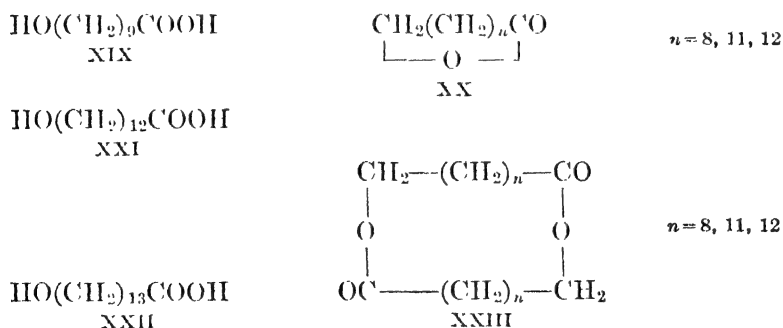
The properties of these esters with regard to fiber formation have been examined.^{22, 25} It was found that by melting or dissolving in chloroform they could be spun into fibers. The filaments were opaque and fragile, but under the influence of a longitudinal stress they underwent elongation and then remained permanently extended. This process was accompanied by a loss of opacity and an increase in tensile strength and pliability. Examination by x-rays showed the presence of fiber orientation. The strongest and most highly oriented fibers were obtained in the case of ω -hydroxydecanoic acid from the esters of approximate molecular weight 17,000–20,000. These were the first examples of synthetic material in the form of fibers which possessed any considerable degree of strength, orientation, and pliability.

It has thus been found possible to produce long, straight-chain polyesters of varying molecular weight, in which the recurring unit is of the type $-\text{O}-(\text{CH}_2)_n-\text{CO}-$. Those acids which may form five-membered cyclic esters ($n = 3$) do not form linear polymers, but always assume a cyclic form. Those acids capable of forming six-membered cyclic esters show a very curious property, i.e., the ability to polymerize and depolymerize in a rather smooth, reversible fashion. This phe-

²⁵ Carothers and Hill, *ibid.*, **54**, 1579 (1932).

nomenon is connected with the ease of hydrolysis of the ester and, like hydrolysis, is hindered by α -substituents. This process probably takes place through an ester-interchange mechanism although small amounts of the free hydroxy acids may be involved. Both forward and reverse reactions are catalyzed by acids and bases, typical ester-interchange catalysts. The reasons for this behavior probably lie in stereochemical factors: rings of six atoms are strained slightly (or may pass through positions of strain), and this strain can be relieved by the formation of a linear molecule through ester interchange. The depolymerization is possible by reason of the high probability of the close approach of atoms in every sixth position in a chain.⁹ These concepts are based on the Sachse-Mohr theory of ring structures.²⁶ It is worth noting that the reversible polymerization of six-membered rings does not occur in the lactam series.

In some cases the linear polyesters derived from the higher hydroxy acids may be depolymerized by the action of heat and an ester-interchange catalyst to many-membered cyclic monomers and dimers; the reverse process may also be carried out in some instances.^{27, 28} This depolymerization has been investigated for a number of polyesters of this class, and it has been found that depolymerizations of linear polyesters from acids such as 10-hydroxydecanoic acid (XIX), 13-hydroxytridecanoic acid (XXI), and 14-hydroxytetradecanoic acid (XXII) yield both monomers (XX) and dimers (XXIII). These depolymeri-



zations are accomplished by heating the polyester with catalysts such as magnesium chloride or stannous chloride to a temperature of 270° under 1 mm. pressure. The yields of monomer are rather high and constitute another synthetic method for the production of macrocyclic lactones. It is interesting to note that the ratio of monomer to dimer in

²⁶ Sachse, *Ber.*, **23**, 1363 (1890); *Z. physik. Chem.*, **10**, 203 (1892); Mohr, *J. prakt. Chem.*, [2] **98**, 315 (1918); [2] **103**, 316 (1922).

²⁷ Hill and Carothers, *J. Am. Chem. Soc.*, **55**, 5031 (1933).

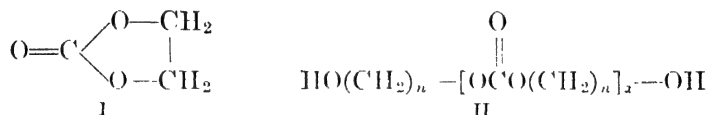
²⁸ Spanagel and Carothers, *ibid.*, **58**, 654 (1936).

case XXII was 15 to 1 while for compound XIX the same ratio was 0.17 to 1.

This curious effect illustrates the greater ease of ring formation in the case of large rings as compared with those of intermediate size.²⁹ It may be that the effect of hydrogen blocking proposed as an addendum to the Sachse-Mohr theory²⁶ by Stoll and Stoll-Comte³⁰ is still partially active in the small ring.

Polyesters from Polybasic Acids and Polyhydric Alcohols. These polyesters are usually referred to as alkyd resins. When both the acid and alcohol are bifunctional, a linear polyester is produced. Higher functionality in either the alcohol or acid leads to the formation of three-dimensional polymers. These are referred to industrially as heat-non-convertible and heat-convertible types, respectively.

Linear Polyesters. The simplest dibasic acid is carbonic acid, and a number of polymeric carbonates have been prepared.^{27, 31} The simplest of the glycol esters, ethylene carbonate, is well known and exists as a monomeric five-membered ring (I).³² The higher carbon-



ates may be prepared by an ester interchange between the glycol and ethyl or butyl carbonate, a reaction which proceeds smoothly in the presence of a catalyst such as metallic sodium. Glycols of the type $\text{HO}(\text{CH}_2)_n\text{OH}$ have been employed in which n ranged from 3 to 14 and also where $n = 18$. The method of preparation indicated a structure shown in II in which the chain was probably open and the terminal groups were either hydroxyls (from the glycol) or carbethoxy (as from ethyl carbonate). Trimethylene carbonate is of particular interest. It may exist either as a monomeric six-membered ring or as a linear polyester in which x is 38-45. Interconversion of the forms was found to proceed readily under the influence of heat and catalysts. This peculiar behavior of six-membered rings has been noted previously. These straight-chain polyesters were powders, with the exception of hexamethylene carbonate, which was obtained in the form of tough, elastic flakes. They were soluble in chloroform, but insoluble in water and alcohol. X-ray diffraction patterns showed definite evidences of crystal-

²⁹ Carothers and Hill, *ibid.*, **55**, 5043 (1933).

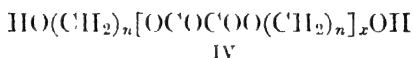
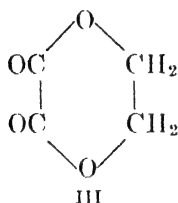
³⁰ Stoll and Stoll-Comte, *Helv. Chim. Acta*, **13**, 1185 (1930).

³¹ Carothers and Van Natta, *J. Am. Chem. Soc.*, **52**, 314 (1930).

³² Vorländer, *Ann.*, **280**, 186 (1894).

linity in all cases. An attempt was made to force depolymerization of these linear esters, and it was found that, under the influence of heat (temperatures between 200–300°) and an ester-interchange catalyst such as sodium, both polymerization and its reverse could be effected. A number of monomeric and dimeric cyclic esters were obtained. Monomers containing rings of seven to twelve atoms were especially difficult to obtain, a fact which is in keeping with the Sachse-Mohr theory²⁶ in its modified form.^{29, 30}

A number of oxalic acid glycol esters have been prepared and studied by Carothers, Arvin, and Dorrough.³³ Ethylene oxalate (III) was



prepared from ethyl oxalate and ethylene glycol, and was found to exist in several forms. The six-membered cyclic monomer (III) was obtained from distillation of the polymer (IV, $n = 2$) *in vacuo*. The monomer is macrocrystalline and may be hydrolyzed very readily. It is partially transformed on standing into a powdery, microcrystalline polymer (IV, $n = 2$). The change is accelerated by moderate heat and catalyzed by acids and alkalies. The polymer hydrolyzes easily. It was obtained in two different forms, one melting at 159° and the other at 172°; the lower-melting material is more soluble than the other variety and has a molecular weight of about 2400. The other is probably a higher form. Samples of intermediate melting points seem to be mixtures of these forms. The polymers show some tendency to depolymerize spontaneously.

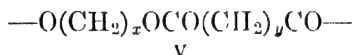
Other oxalates prepared were the propylene, trimethylene, hexamethylene, and decamethylene esters. The propylene ester was found to exist both as a monomer and a linear polymer which were interconvertible by heat. Polymerization was less rapid than in the case of ethylene oxalate. The three others were polymeric forms which resembled the linear polyesters previously obtained. These white powders were subjected to depolymerization conditions and monomers of the higher esters were obtained,²⁷ while a dimer of trimethylene oxalate was found.³³

Other esters of this general nature have been prepared,³⁴ including

³³ Carothers, Arvin, and Dorrough, *J. Am. Chem. Soc.*, **52**, 3292 (1930).

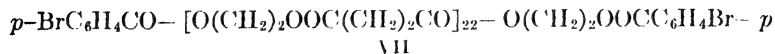
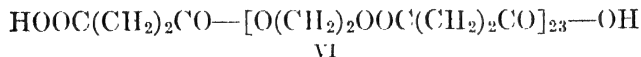
³⁴ Carothers and Arvin, *ibid.*, **51**, 2560 (1929).

ethylene malonate, ethylene succinate, trimethylene succinate, ethylene adipate, trimethylene adipate, hexamethylene succinate, hexamethylene adipate, ethylene sebacate, trimethylene sebacate, decamethylene succinate, hexamethylene sebacate, decamethylene adipate, decamethylene sebacate, ethylene maleate, ethylene fumarate, ethylene phthalate, trimethylene phthalate, hexamethylene phthalate, and decamethylene phthalate. These esters probably exist in the polymeric form as long chains. All of them of the type V are microcrystalline solids with the



exception of ethylene malonate. The melting points are not very sharp and are dependent somewhat on the rate of heating. Molecular weights vary from 2300 to 5000. All the esters are quite viscous when molten. The phthalate esters are resinlike, and were not obtained in a crystalline form. All the esters are non-volatile, and are insoluble or nearly so in water, alcohol, petroleum ether, and ether. They are all somewhat hygroscopic. These higher esters may be depolymerized by heating at 270° under 1 mm. pressure for several hours in the presence of a catalyst such as stannous chloride or magnesium chloride to yield cyclic monomers or dimers.³⁵ This reaction affords a good method for preparing these.

Ethylene succinate, one of the simpler esters, was investigated with the view of determining the structure.³⁶ This polyester was prepared by heating a mixture of the acid and the glycol and finally removing the excess glycol by distillation *in vacuo*. The neutral ester, of molecular weight about 3000, was shown to be a linear structure with glycol hydroxyls acting as terminal groups. These hydroxyls were not esterified by acetic anhydride, but succinic and *p*-bromobenzoic anhydrides provided the expected products when the reaction was carried out at an elevated temperature. The products had compositions agreeing with formulas VI and VII.



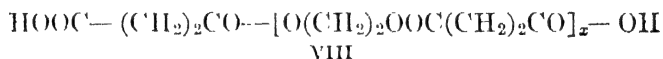
It was found that polymerization could proceed by a process of ester interchange, since di-(β -hydroxyethyl) succinate was transformed into

³⁵ Spanagel and Carothers, *ibid.*, **57**, 929 (1935).

³⁶ Carothers and Dorough, *ibid.*, **52**, 711 (1930).

the neutral polymer on heating. A number of these di-(β -hydroxyethyl) esters have been prepared by Shorland³⁷ by heating an excess of ethylene glycol with the acids at 100°. On warming to 160° they polymerize slowly, and on heating to 260° they are converted to the polyesters previously observed. This indicates that large molecules may be built up through an ester-interchange reaction. A dimeric product was also found by Carothers *et al.*³⁶ to exist as a many-membered ring. This was obtained in small amounts as one of the products of thermal decomposition of the linear polyesters. It was also found possible to obtain superpolyesters from the lower polymers. These high-molecular-weight polymers exhibited the property of forming fibers that changed from opaque, brittle filaments to transparent, oriented, tough fibers on being subjected to cold drawing. This property does not appear until the molecular weight reaches about 9000. For a useful degree of strength and pliability a molecular weight of about 12,000 and a molecular length of not less than 1000 Å seem requisite.²⁵

The acidic polymeric ethylene succinates were also prepared. Heating the glycol with an excess of the acid produced linear esters in which the degree of polymerization varied from 6 to 23. These esters were acidic in reaction, and were of the general form VIII in which succinic



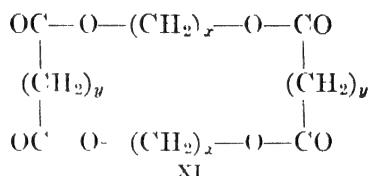
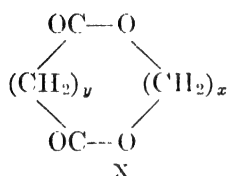
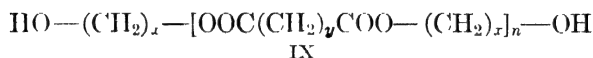
acid residues occupy the end groups. It should be emphasized that high-molecular-weight polyesters can be obtained only by use of pure glycols and pure dibasic acids in exactly equimolecular amounts. It was the realization of the importance of these two factors by Carothers that enabled him to set up conditions which would produce useful polyesters.

The general properties of these linear polyesters may be summarized briefly. They are generally microcrystalline powders of varying molecular weight. Adoption of a stringent reaction environment results in the formation of superpolyesters of molecular weights up to about 25,000. Certain molecular ranges provide polymers which exhibit the phenomenon of cold-drawing. All the polyesters are quite viscous in the molten state. Volatility decreases with increase in molecular size partly owing to the increase in intermolecular forces. In general, compounds with molecular cohesions above 75,000 calories cannot be dis-

³⁷ Shorland, *ibid.*, **57**, 115 (1935).

titled, and molecular cohesions of the polyesters, which have been calculated as 250,000 to 300,000 calories³⁸ from the data of Meyer,³⁹ are far above this value.

Depolymerization can be effected very easily if the monomeric unit ester is a six-membered ring, but under more stringent conditions the polymers of the general type (IX) are subjected to an ester-interchange reaction and obtained as monomers (X) or dimers (XI). The carbonates and oxalates undergo this change more readily than the higher acid esters.



Three-Dimensional Polyesters. If one of the molecular species employed in the esterification reaction contains more than two functional groups, a new type of polymer results, and the properties of these polymers are totally different from the previously encountered linear polymeric esters prepared from dibasic acids and dihydric alcohols. As representative of the difference between the two types of polymers, the reaction products of phthalic anhydride with ethylene glycol and glycerol serve admirably for illustration. The reaction of phthalic anhydride with ethylene glycol has been studied by Kienle and Hovey.⁴⁰ The reaction is a simple esterification which under the usual conditions goes very rapidly at the start. The number of reactive groups grows lower near the end of the reaction. The acidity decreases and the molec-

| TEMPERATURE, °C. | TIME AT WHICH ESTERIFICA- TION = 95 PER CENT, minutes |
|---------------------|---|
| 190 | 1000 |
| 220 | 220 |
| 230 | 145 |
| 250 | 55 |

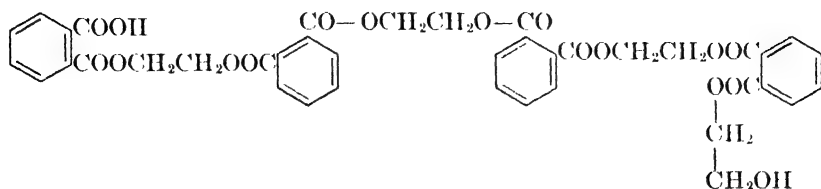
ular weight and viscosity rise. The dependence on temperature is shown in the table. The polymer is unable to undergo cross-linking,

³⁸ Carothers and Arvin, *ibid.*, **51**, 2560 (1929).

³⁹ Meyer, *Z. angew. Chem.*, **41**, 943 (1928).

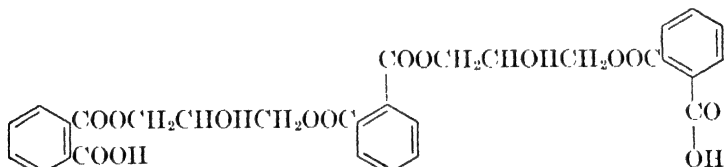
⁴⁰ Kienle and Hovey, *J. Am. Chem. Soc.*, **52**, 3636 (1930).

and the final product is similar to XII. The end groups may be carboxyls or hydroxyls. The properties change slowly and continuously with increasing molecular size.



XII

When glycerol is substituted for ethylene glycol, a new feature is introduced. This reaction has been studied by Kienle and co-workers, who have also investigated the reaction between glycerol and other dibasic acids such as succinic, adipic, and sebacic.^{41, 42} Temperatures in the neighborhood of 200° were employed. The reaction between phthalic anhydride and glycerol was strongly exothermic at the beginning and was about one-half completed at the end of one minute. This probably was the stage where the anhydride was used up and thereafter esterification involved reaction of a carboxyl group and a hydroxyl group. When the esterification was about 75–79 per cent complete, gelation occurred. These steps have been interpreted by Hönel⁴³ and by Schlenker.⁴⁴ The first-stage esterification reaction occurs with the α -hydroxyl groups of the glycerol, and the polyesters formed retain a linear structure. This is in agreement with the evidence that the



XIII

α -hydroxyl groups of glycerol are more reactive than the β -hydroxyl.⁴⁵ Continuation of the reaction, however, necessitates the entry of the β -hydroxyl groups into ester linkages. When this occurs a three-dimensional molecule results as a consequence of cross-linking:

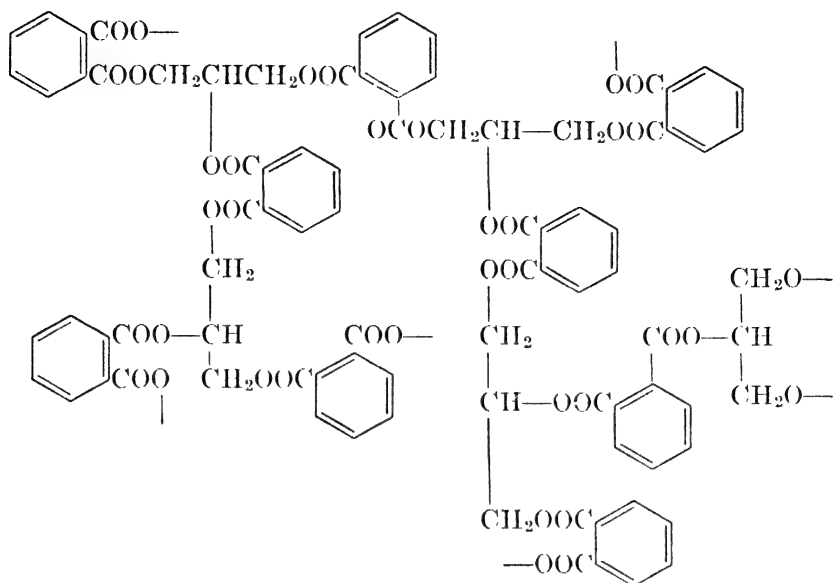
⁴¹ Kienle and Hovey, *ibid.*, **51**, 509 (1929).

⁴² Kienle, van der Meulen, and Petke, *ibid.*, **61**, 2258, 2268 (1939); Kienle and Petke, *ibid.*, **62**, 1053 (1940); **63**, 481 (1941).

⁴³ Hönel, *Kunststoffe*, **21**, 76, 105, 132 (1931).

⁴⁴ Schlenker, *Allgem. Oel- u. Fett-Ztg.*, **29**, 658 (1932).

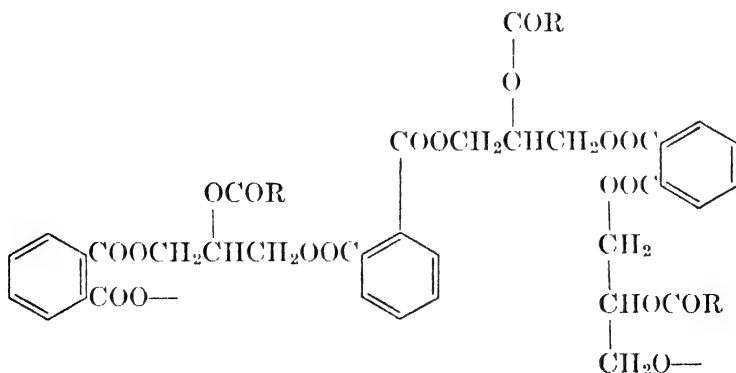
⁴⁵ Fairbourne and Cowdrey, *J. Chem. Soc.*, 129 (1929).



XIV

The formation of these high-molecular-weight three-dimensional molecules is responsible for the gelation of the polymer and gives it the quality of heat-convertibility. These macromolecules are both infusible and insoluble, and the degree to which the resin possesses these properties is related to the number of these high-molecular-weight molecules which are present. An excess of phthalic anhydride over glycerol should be effective in producing a greater degree of cross-linking, and such an effect has been found.⁴⁶

The properties of these polymers may be modified by the introduction of a monobasic acid. If an excess of phthalic anhydride is avoided, the addition of a monobasic acid followed by heating to complete esterification will result in a molecule of the type (XV) which is an



XV

⁴⁶ Sugimoto, *Repts. Imp. Ind. Research Inst., Osaka, Japan*, **14**, (13) 11 (1933).

approximation of a linear molecule. In practice, ester-interchange reactions compete with straight esterification, and gelation due to cross-linking usually stops further reactions.

Many modifications of this reaction exist. For example, if an unsaturated long-chain acid is used as the monobasic acid, the resultant polymer may undergo a further degree of polymerization through a "drying" mechanism similar to that observed in the drying oils. Incorporation of other polymers or plasticizers is frequently necessary to produce commercial products of the required nature.

The use of many other acids and alcohols has been proposed. Many of these are noted by Ellis.⁴⁷ For example, pentaerythritol and the sugar alcohols, sorbitol and mannitol, have been employed with phthalic anhydride or other acids to produce plastics. Wide variations are possible, depending on the commercial use for which the polymer is designed. Garvey, Alexander, K \ddot{u} ng, and Henderson⁴⁸ have made some rubberlike mixed polymers by vulcanizing polyethylene tartrate by cross-esterification of its hydroxyl groups with a little succinic acid.

Polyamides

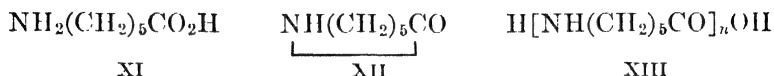
The polymeric amides may be divided into two classes in the same fashion as the polyesters. In one of these classes may be placed those amides derived from amino acids; the second group will comprise those polymers formed from two or more molecular species, as polybasic acids and polyfunctional amines. Their properties and structures are in general related to the esters which have already been discussed. Their importance, however, lies in their relation to the most important of the great groups of naturally occurring macromolecules, the proteins. The chemical properties of the amide linkage, upon which the structure of the proteins is based, are exemplified by the behavior of the simple polymeric amides. The problem of protein structure, however, is more difficult than would be suggested by elementary studies of these compounds. Polypeptides have often been prepared in the laboratory, but no protein has ever been synthesized. It has been generally accepted that proteins are macromolecules made up of more or less complex amino acids bound together through amide linkages. As such, they may be regarded as macromolecules derived from a mixture of amino acids through a process of condensation copolymerization.

⁴⁷ Ellis, "The Chemistry of Synthetic Resins," Vol. II, Reinhold Publishing Corp., New York (1935).

⁴⁸ Garvey, Alexander, K \ddot{u} ng, and Henderson, *Ind. Eng. Chem.*, **33**, 1060 (1941).

The β -amino acids do not form polymers on heating but lose ammonia. The γ - and δ -amino acids readily pass into the corresponding lactams, and neither the five- or six-membered lactams show a tendency to rearrange to polymeric amides.

ϵ -Aminocaproic acid (XI) on heating gives a mixture of cyclic lactam (XII) and polymer (XIII).⁵⁸ The lactam exists to the extent of 6–10



per cent in the equilibrium mixture. The polymer is a white wax, insoluble in most organic solvents except formic acid or phenol. It is soluble in hot formamide, from which it separates as a microcrystalline powder. The molecular weight is in the range of 800–1200, indicating about 10 units in the chain (XIII, $n = 10$). The nature of the end groups is not definitely known, but presumably the amino group is present, since derivatives with acid chlorides and anhydrides are obtained. The polymer is alkali-insoluble. Heating this polymer in a molecular still at 200° for forty-eight hours gives a distillate of lactam, and the residual polymer becomes harder and tougher.⁵⁹ No data on molecular weight have been reported on this modified product.

ζ -Aminoheptioic acid gives a polymer⁶⁰ when heated, and this polymer is reported to be soluble in mineral acids and hot aniline. Extensive studies have shown that the higher amino acid polymers⁶¹ have the same solubility as the polymer from ϵ -aminocaproic acid. They do show different melting points.

Polyamides from Diamines and Dibasic Acids. Amide formation between dibasic acids and diamines has been reported many times in the older literature but the products received little attention.⁶² Some of these substances were low-molecular-weight cyclic amides, and some were infusible and insoluble, indicating their polymeric nature.

A detailed investigation of the formation of polymeric amides from diamines and dibasic acids was carried out by Carothers.⁶³ Substantially equimolecular amounts of a diamine and a dicarboxylic acid or an

⁵⁸ Gabriel and Maass, *Ber.*, **32**, 1266 (1899); Carothers and Berchet, *J. Am. Chem. Soc.*, **52**, 5289 (1930); U. S. patents, 2,241,321; 2,241,322; 2,241,323 (1941).

⁵⁹ Carothers and Hill, *J. Am. Chem. Soc.*, **54**, 1566 (1932).

⁶⁰ Manasse, *Ber.*, **35**, 1367 (1902); v. Braun, *Ber.*, **40**, 1834 (1907).

⁶¹ Carothers, U. S. patent, 2,071,253 (1937).

⁶² Fischer and Koch, *Ann.*, **232**, 227 (1886); Hofmann, *Ber.*, **5**, 247 (1872); Freund, *Ber.*, **17**, 137 (1884); Anderlini, *Gazz. chim. ital.*, **24**, (1) 397, (1894); *Ber.*, **27R**, 403, 404 (1894); Fischer, *Ber.*, **46**, 2504 (1913); Meyer, *Ann.*, **347**, 17 (1906); Ruggli, *Ann.*, **392**, 92 (1912); Butler and Adams, *J. Am. Chem. Soc.*, **47**, 2614 (1925).

⁶³ Carothers, U. S. patents, 2,130,523; 2,130,947; 2,130,948 (1938).

amide-forming derivative of the acid were heated under condensation conditions at temperatures between 180° and 300° in the presence or absence of a diluent. The amides to which the greatest interest was attached were those in which methylene groups in chains of varying length separated the functional groups. The molecular weight of the product depended upon the conditions imposed during the reaction. Under prolonged heating with suitable arrangements for escape of the volatile products of the condensation, the molecular weight reached large values. No method was available for exact estimation of these values, but the range was very probably of the same magnitude observed for the polyesters obtained from glycols and dibasic acids. The size of the molecule, however, could be controlled within limits by using either of the reactants in slight excess. The amount used in excess determined in each case the extent of the reaction. Since the reaction was essentially stopped under these conditions, the viscosity of solutions of the polymer assumed a constant value that was not altered appreciably on further heating. Hence, the excess reactant was referred to as a "viscosity stabilizer" and these polymers as *viscosity-stable-polymers*.

The reaction may be carried out in a number of fashions. One convenient method is to prepare the salt by combination of approximately equal amounts of the acid and amine. If a suitable solvent is employed, the acid and amine may be used in solution and the salt obtained as a crystalline precipitate. Such a procedure is possible with hexamethylenediamine and adipic acid; an alcohol-water mixture may be employed as the solvent. These salts are relatively insoluble in acetone, benzene, and ether, but they are usually soluble in water. Recrystallization of the salts may be effected if necessary. The simplest means of obtaining the polymer is to heat the salt under fusion conditions (180–300°) in the absence of oxygen.⁶⁴

The polyamides so produced generally have high melting points and low solubilities. They are usually soluble in hot glacial acetic acid, formic acid, and phenols, but insoluble in the other common organic solvents. However, if side chains are present, as in the products from 3-methylhexamethylenediamine, β -methyladipic acid, and similar compounds, the polyamides become soluble in a wider range of solvents, including some alcohols. This is also true of copolymers. The polyamides are also soluble in anhydrous hydrofluoric acid. Hot acids such as sulfuric or hydrochloric hydrolyze the amides to the component acids and bases. Strong alkali will also bring about hydrolysis. The melting points of these polyamides are somewhat uncertain, owing to variations in methods of preparation, but under the same conditions they are fairly

⁶⁴ Graves, U. S. patent, 2,165,253 (1939).

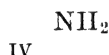
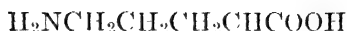
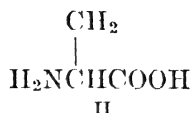
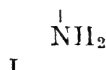
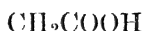
sharp and reproducible. In general, the melting points decrease with increase in unit length of hydrocarbon chain and with substitution. Some of these melting points are shown in the table.

| POLYAMIDE FROM | M.P., °C. |
|-------------------------------------|-----------|
| Ethylenediamine; sebacic acid | 254 |
| Tetramethylenediamine; adipic acid | 278 |
| Tetramethylenediamine; azelaic acid | 223 |
| Pentamethylenediamine; malonic acid | 191 |
| Pentamethylenediamine; adipic acid | 223 |
| Pentamethylenediamine; azelaic acid | 178 |
| Hexamethylenediamine; adipic acid | 263 |
| Hexamethylenediamine; sebacic acid | 209 |
| Octamethylenediamine; sebacic acid | 197 |
| Decamethylenediamine; oxalic acid | 229 |
| Piperazine; sebacic acid | 153 |

Those polyamides with a molecular weight above about 7000 are particularly useful since they possess the unusual property of forming strong fibers. Filaments may be obtained from a molten mass of the polyamide by an extrusion method. They are also obtained from solutions of polyamides by extrusion into a heated chamber for solvent evaporation, or into a bath of some liquid miscible with the solvent but a non-solvent for the polymer. Phenol solutions of polyamides can be used with an aqueous alkaline spinning bath, and formic acid solutions can be used for the evaporation process. The filaments are then subjected to cold-drawing, i.e., stretching. Under the influence of this stress the fiber becomes oriented and takes on a high degree of strength along the axis of the stress. The orientation is evidenced by x-ray studies showing a fiber diffraction pattern. These fibers are also optically anisotropic: a strong birefringence with parallel extinction may be observed under crossed Nicol prisms. The extent of cold drawing may be 100 per cent or higher (200–250 per cent); failure in one instance did not occur until an elongation of 452 per cent. The resulting fibers are quite elastic and tough, and retain a high wet-strength. Their properties thus make them extremely attractive from the commercial point of view. Polyamides of this type are called “nylons” and are being marketed as fibers. These polyamides are also being used for the manufacture of bristles.

There is no well-developed field of polymeric amides corresponding to the alkyd resins. Such compounds are possible, of course, but no detailed investigation of their properties has appeared. There are, however, a number of naturally occurring polyfunctional amino acids, such as lysine (I), glutamic acid (II), serine (III), and ornithine (IV), which on complete condensation would yield branched-chain polymers.

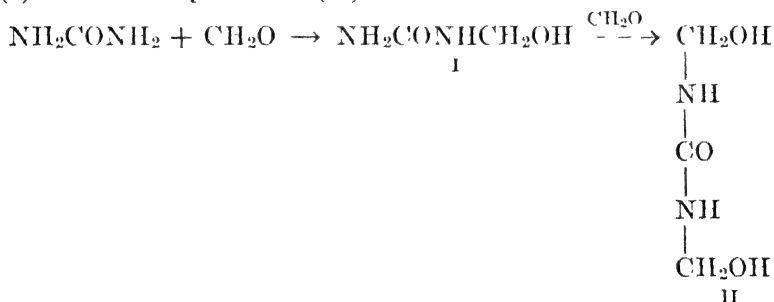
Some of these cross-linked polymers may perhaps exist in nature, but they are at present unimportant as synthetic polymers.



Urea-Formaldehyde Polymers

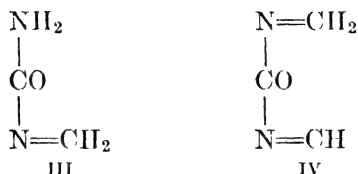
The urea-formaldehyde resins are very important since they are made from low-cost raw materials, have good thermosetting properties, excellent color, attractive appearance, and good life. They have received much scientific study, but the reaction of their formation is still not completely understood. Many intermediate products have been isolated and characterized by the investigators of this reaction,⁶⁵ but it is not certain now that all these products are chemical individuals or that they are formed in the normal polymerization process.

It is now generally believed that urea and formaldehyde react reversibly in the presence of acid and basic catalysts to produce methylol urea (I) and dimethylol urea (II).



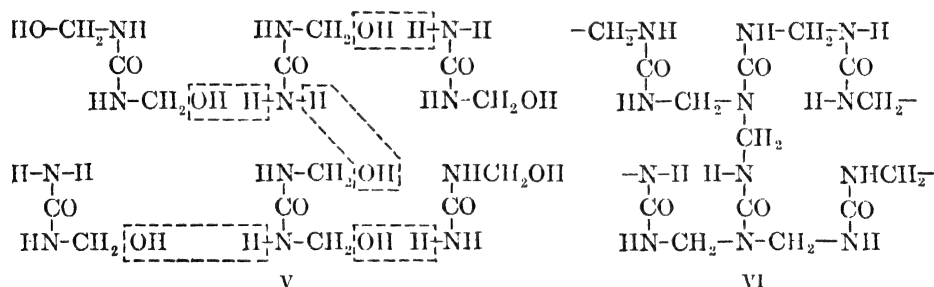
⁶⁵ Goldschmidt, *Ber.*, **29**, 2438 (1896); Hölzer, *Ber.*, **17**, 659 (1884); **18**, 3302 (1885); Ludy, *Monatsh.*, **10**, 295 (1889); *J. Chem. Soc.*, **56**, 1059 (1889); Tollens, *Ber.*, **29**, 2751 (1896); Einhorn, *Ann.*, **361**, 113 (1908); Einhorn and Hamburger, *Ber.*, **41**, 24 (1908); Hodgins and Hovey, *Ind. Eng. Chem.*, **30**, 1021 (1938); **31**, 673 (1939); Kadowaki, *Bull. Chem. Soc. Japan*, **11**, 248 (1936); *Repts. Imp. Ind. Research Inst., Osaka, Japan*, **7**, No. 6 (1926); **13**, No. 3, No. 6 (1932); **14**, No. 6 (1933); **14**, No. 11 (1934); **16**, No. 6 (1935); Hemmelmayr, *Monatsh.*, **12**, 94 (1891); Dixon, *J. Chem. Soc.*, 238 (1918); Scheibler, Trostler, and Scholz, *Z. angew. Chem.*, **41**, 1305 (1928); van Laer, *Bull. soc. chim. Belg.*, **28**, 381 (1919); Staudinger, *Ber.*, **59**, 3019 (1926); Walter and Oesterreich, *Kolloid-Beihfte*, **34**, 115 (1931); Walter and Lutwak, *ib id.*, **40**, 158 (1934); Walter, *Kolloid-Z.*, **57**, 229 (1931); Walter and Gewing, *Kolloid-Beihfte*, **34**, 163 (1931); Walter, *Trans. Faraday Soc.*, **32**, 377 (1936); de Chesne, *Kolloid-Beihfte*, **36**, 387 (1932); Redfann, *Brit. Plastics*, **5**, 238 (1933); Ellis, U. S. patent, 2,115,550 (1938).

Further heating of either of these products results in polymer formation. This may occur by dehydration of the monomers to give methylene (III) and dimethylene urea (IV) which then polymerize by an addition mechanism.

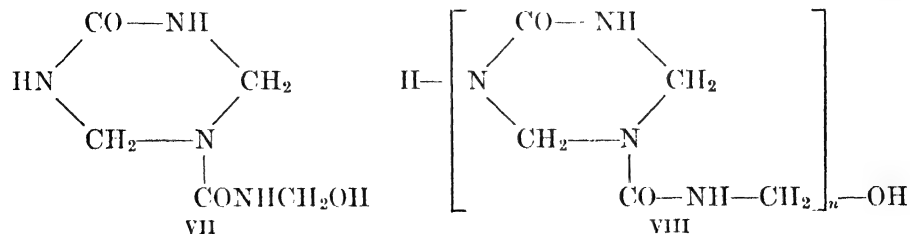


The dimethylene urea would be the constituent of the polymerization mixture which would cause cross-linking. More probably, however, the polymerization proceeds by a stepwise loss of water between the molecules of methylol and dimethylol urea. On this basis the dimethylol urea is responsible for the cross-linking. It is known that methylol urea liberates formaldehyde on heating, and this may combine with more methylol urea to give dimethylol urea. Hence the polymer produced from pure methylol urea as a starting material will still be very complex.

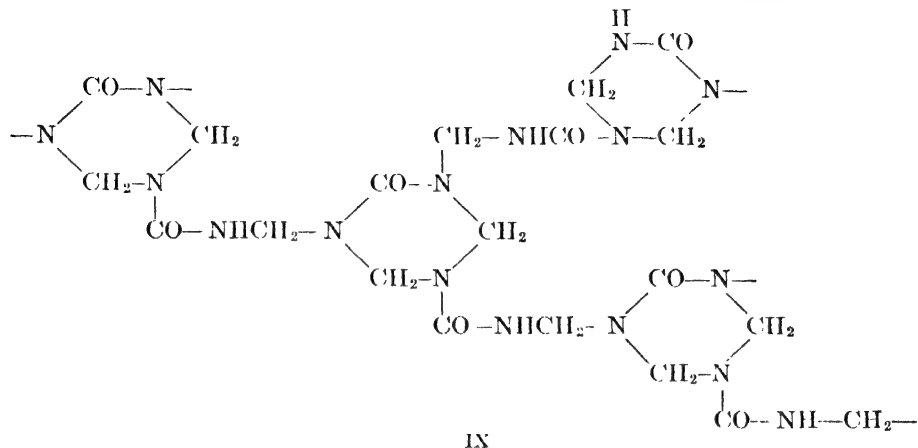
No strictly accurate scheme for this polymerization reaction can be written, but the following may be considered a possible route from methylol and dimethylol urea (V) to the final cross-linked polymer (VI).



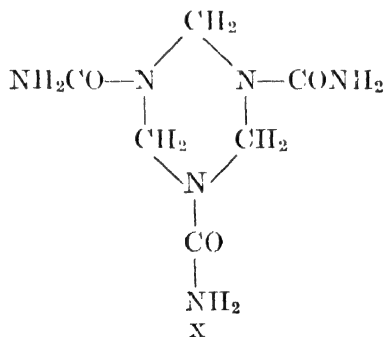
Another possible intermediate is a cyclic derivative (VII) which could react with itself to produce a polymer with the six-membered ring in its recurring unit (VIII). Cross-linking, which can also occur in this



type (IX) of intermediate, would account for the insolubility and infusibility of the final polymer. Recently, it has been suggested ⁶⁶ that



methylene urea (III) may trimerize through the methylene-imine groups and that this trimer (X) may then react further with formaldehyde to give new methylene-imine groups which in turn form six-



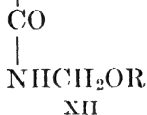
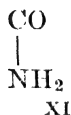
membered rings. This picture of the reaction accounts for the high degree of branching and cross-linking which occurs in the resins of this type.

Whatever the exact method of condensation, urea-formaldehyde polymers can be made which are water-soluble. Heating these produces a glasslike gel, and further heating gives the well-known product of commerce. The water-soluble resins are widely used in treating textiles. The powders are used as molding resins.

Another recent variation in the formation of the final polymer is the use of the ethers of the monomethylol (XI) or dimethylol derivatives

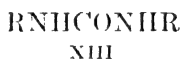
⁶⁶ J. T. Thurston, "Chemistry of Melamine Resins," Gibson Island Conference on Polymeric Materials (1941).

(XII) of urea,⁶⁷ which are easily made by carrying out the condensation of urea and formaldehyde in the presence of an alcohol. These ethers

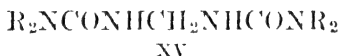


undergo condensation polymerization to produce essentially the same polymers as the methylol derivatives themselves.

It is of interest to note that neither symmetrical⁶⁸ nor unsymmetrical dialkyl ureas give polymeric materials with formaldehyde. With the symmetrical derivatives (XIII) a product is formed from two molecules of the urea and two of formaldehyde with the loss of one molecule of

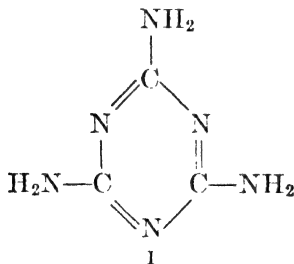


water. The unsymmetrical derivative (XIV) gives a methylene diurea (XV).



Melamine-Formaldehyde Polymers

The melamine-formaldehyde resins are similar to those derived from urea and formaldehyde. Melamine is 2,4,6-triamino-1,3,5-triazine (I) and is prepared commercially from cyanamide through the inter-



mediate formation of dicyandiamide.⁶⁹ It may be condensed with formaldehyde to form melamine methylol derivatives, and these may

⁶⁷ Hodgins and Hovey, *Ind. Eng. Chem.*, **31**, 673 (1939); Sorenson, U. S. patent, 2,191,974 (1940).

⁶⁸ Scheibler, Trostler, and Scholz, *Z. angew. Chem.*, **41**, 1305 (1928).

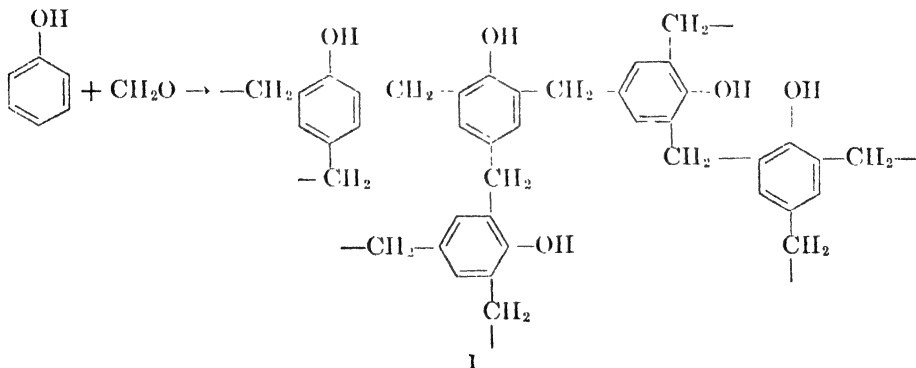
⁶⁹ McClellan, *Ind. Eng. Chem.*, **32**, 1181 (1940).

be heated to form thermosetting polymers.⁷⁰ The reaction is probably similar to that between urea and formaldehyde.^{66, 71}

These polymers have recently become commercially important because of their superior stability to heat and light. They are used in molding resins under the trade name "Beetle-Melamine" and also, incorporated with alkyd resins, in quick-curing enamels under the trade name "Melamac."

Phenol-Aldehyde Polymers

The reaction between phenols and aldehydes was apparently first investigated by Baeyer and his students in 1872.⁷² Many other workers have added to the knowledge of this condensation reaction in the intervening years. Around 1900, patents began to appear on these products, but it remained for Baekeland⁷³ to demonstrate the possibilities of the reaction from a practical point of view. The resins first used were made by condensing phenol and formaldehyde with either acid or alkaline catalysts. Alkaline catalysts bring about the condensation of formaldehyde in the *ortho* and *para* positions of phenol, and this reaction has essentially the same chances of producing a three-dimensional resin as the glycerol-phthalic anhydride combination. The two positions of the methylene radical ($-\text{CH}_2-$) correspond to those of the anhydride, and the three positions in the phenol ring correspond to those in glycerol. A possible type of polymer is shown in I, but many variations can be written. That the hydroxyl groups are not concerned in this reaction is



⁷⁰ Soc. pour l'ind. chim. à Bâle, French patent, 811,804 (1937); British patents, 468,677; 468,746 (1937); British patents, 486,519; 486,577 (1938); Swiss patents, 197,486-91 (1938); Deutsche Hydrierwerke A.-G., British patent, 502,720 (1939); Sanderson, *Paint, Oil Chem. Rev.*, **102**, No. 8, 7 (1940).

⁷¹ Hodgins, Hovey, Hewett, Barrett, and Meeske, *Ind. Eng. Chem.*, **33**, 769 (1941).

⁷² Baeyer, *Ber.*, **5**, 25, 280, 1094 (1872).

⁷³ Baekeland, U. S. patent, 942,809 (1909); *J. Ind. Eng. Chem.*, **1**, 149, 545 (1909); **3** 518, 932 (1911); **4**, 737 (1912); **5**, 506 (1913).

indicated by the fact that the low-molecular-weight resins first produced are alkali-soluble.

By use of a phenol substituted in the *ortho* or *para* position, the possibilities for cross-linking disappear. By mixing a certain amount of such a substituted phenol with phenol itself, the properties of the final polymer can be greatly changed somewhat as glycerol-phthalic anhydride esters can be modified by introducing a certain amount of mono-basic acid with the dibasic acid. A position in the ring cannot be blocked with a methylol group as these can leave the ring as well as enter it under alkaline reaction conditions.

Acid catalysts cause a slightly different type of polymer to form. Even the low-molecular-weight products first obtained are alkali-insoluble. Thus the phenolic hydroxyl must be used up, and this may be the result of ether formation between neighboring phenol groups or acetal formation. In either of these events we have a 2-4 combination rather than the 2-3 combination discussed in the case of the alkaline-catalyzed reaction.

The thermosetting properties of both the urea-formaldehyde and the phenol-formaldehyde resins are possible because the condensation reactions produce the methylol intermediates, $-CH_2OH$. Further heating causes still further condensation to occur until the infusible state is reached. Oil-soluble phenolic resins prepared from substituted phenols for use in varnishes have recently been reviewed by Turkington and Allen.⁷⁴

Other aldehydes and other phenols are used industrially for certain resins. Aromatic amines may be used in place of phenols, and the "Ciba" type resins result. However, they are formed by essentially the same sort of complex condensation reactions as have been pictured above. In the case of the amines the aldehyde also attacks the nitrogen atom, thus increasing the possible complexity of the final polymer.⁷⁵ The *meta*-phenylenediamine-formaldehyde polymer has found some use in the removal of anions from water.⁷⁶

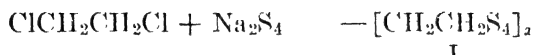
⁷⁴ Turkington and Allen, *Ind. Eng. Chem.*, **33**, 966 (1941).

⁷⁵ See Sprung, *Chem. Rev.*, **26**, 297 (1940), for a general review of the reaction of amines and aldehydes.

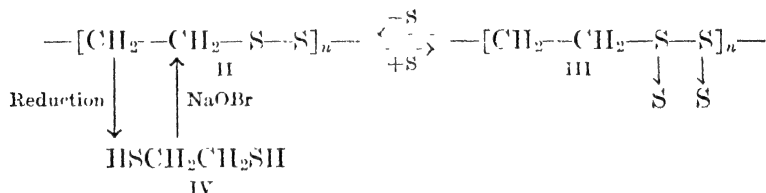
⁷⁶ Adams and Holmes, *J. Soc. Chem. Ind.*, **54**, 1 6T (1935); Schwartz, Edwards, and Boudreaux, *Ind. Eng. Chem.*, **32**, 1462 (1940); Myers, Eastes, and Myers, *ibid.*, **33**, 697 (1941).

“Thiokols”

Ethylene chloride and sodium polysulfide react on heating to give a polymeric polysulfide with properties resembling those of rubber (I).⁷⁷



The polymeric molecule has been converted⁷⁸ to a polyethylene disulfide (II) which will again take up sulfur to give the rubberlike product (III). The polyethylene disulfide has been reduced to ethylene dimercaptan (IV). The structure (III) of the polymer has been demonstrated not



only by the degradation mentioned but also by synthesis. Ethylene dimercaptan (IV) has been oxidized to an ethylene disulfide polymer which on treatment with elemental sulfur has given a product apparently identical with the polymer described above (III).

The nature of the polymer depends on the proportions of reacting materials. To get the tough rubbery product, the sodium polysulfide must be used in excess. If ethylene chloride is in excess, the polymer is a viscous liquid. This second polymer is of a much lower molecular weight than the former. A reasonable explanation for this is apparent. If excess polysulfide is used the end groups are undoubtedly ---SH by breakdown of the ---S---S---Na units. Since sodium tetrasulfide will



oxidize an ---SH group to an ---S---S--- group, this reaction may be responsible for polymer formation when an excess of polysulfide is used, and the molecule can continue to grow in this way as well as by the primary reaction. The $\text{---CH}_2\text{CH}_2\text{Cl}$ end group can react in only one way to cause increased molecular weight.

The condensation products obtained when excess sodium polysulfide is used may be vulcanized, usually with zinc oxide and water. It seems likely that this process is responsible for further increase in chain length due to oxidation of terminal ---SH groups and formation of more disulfide units. Vulcanization of rubber is thought to involve a low degree of

⁷⁷ Patrick, U. S. patent, 1,890,191 (1932).

⁷⁸ Martin and Patrick, *Ind. Eng. Chem.*, **28**, 1141 (1936); Patrick, *Trans. Faraday Soc.*, **32**, 347 (1936).

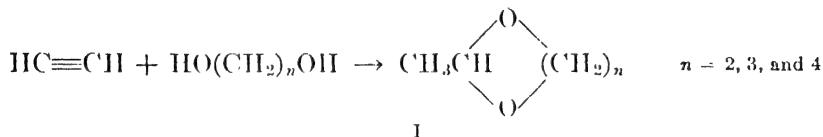
cross-linking of the long linear molecules. It is difficult to see how cross-linking is involved in the vulcanization of the "thiokols."

The ethylene "thiokols" are probably the most important practically, but many others have been prepared from such products as trimethylene chloride, dichlorodiethyl ether, and propylene chloride.

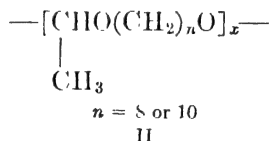
Polyacetals

By far the most important polyacetals are the naturally occurring ones such as cellulose, starch, and inulin, which are discussed elsewhere in this book (Chapter 22). However, as considerable work has been done on synthetic products of this type, a few examples of them will be discussed.

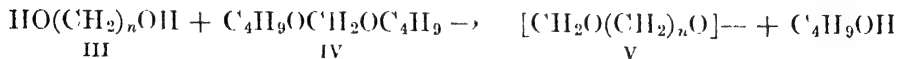
H. S. Hill and Hibbert⁷⁹ have investigated acetal formation when glycols are treated with acetylene. They found that the lower glycols give five-, six-, and even seven-membered rings (I). The six-membered



rings formed most readily, the five-membered rings next, and the seven-membered rings were most difficult to obtain. When octamethylene glycol and decamethylene glycol were used in the reaction, heavy, syrupy, odorless acetals of high and indefinite boiling points were obtained. These were undoubtedly linear polyacetals (II).



Hill and Carothers⁸⁰ studied the formation of acetals (V) from glycols (III) and dibutyl formal (IV) with an acid catalyst. The polymers



obtained directly by this reaction have a molecular weight of around 2000. Heating in a molecular still converts them to higher polymers and to cyclic monomeric or dimeric acetals. The polymers obtained by this procedure can be oriented by cold-drawing to give filaments.

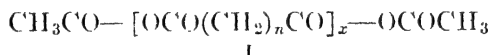
⁷⁹ H. S. Hill and Hibbert, *J. Am. Chem. Soc.*, **45**, 3108, 3117, 3124 (1923).

⁸⁰ Hill and Carothers, *ibid.*, **57**, 925 (1935); Carothers, U. S. patent, 2,110,499 (1938).

Other Condensation Polymers

In addition to the polymer-forming reactions, which have received greater attention because of the practical importance of the products, many others have been studied academically. Many of these are of as much theoretical interest as the reactions already discussed. Since they follow the general patterns which have been discussed, however, it is not necessary to go into great detail here.

The formation of anhydrides from dibasic acids was given special attention by Hill and Carothers,⁸¹ although many polymeric products had been incompletely described in the older literature. The recent work on the anhydrides of the series $\text{CO}_2\text{H}(\text{CH}_2)_n\text{CO}_2\text{H}$, in which $n = 4, 5, 6, 7, 8, 9, 10, 11, 12$, and 16, has shown that they are all linear polymers when prepared by the action of acetic anhydride or acetyl chloride on the dibasic acid. The reaction of these polymers with aniline proved to be very useful in distinguishing them from dimeric cyclic products and as a means of showing that the end groups were acetyl (I). The end groups give some acetanilide whereas the anhydride units in the chain react in a random fashion to produce dianilide, monoanilide,



and dibasic acid according to the laws of chance. These require that, for every molecule of dibasic acid in the chain, one-half molecule of monoanilide, one-quarter molecule of dianilide, and one-quarter molecule of dibasic acid shall be formed. The experimental results checked this as well as could be expected for these large molecules.

Polymeric anhydrides can be depolymerized to give cyclic monomers or dimers. In the series of polymeric anhydrides studied by Hill and Carothers,⁸¹ polysuberic, polysebacic, and polydodecanoic anhydrides, when depolymerized by heating in a molecular still, gave dimeric anhydrides having 18, 22, and 26 members in the rings. All the other poly-anhydrides in that series gave monomeric cyclic anhydrides, but the ten- and twelve-membered rings were extremely unstable and tended to revert to the linear polymer form except at liquid-air temperatures.

Reactions which should produce polyamines, such as those of an alkylene dibromide and ammonia,^{82, 83, 84} aliphatic dibromides and

⁸¹ Hill, *J. Am. Chem. Soc.*, **52**, 4110 (1930); Hill and Carothers, *ibid.*, **54**, 1569 (1932); **55**, 5023 (1933).

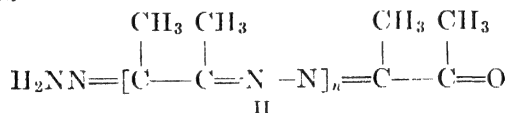
⁸² Hofmann, *Ber.*, **3**, 762 (1870); **4**, 666 (1871); **23**, 3297, 3711 (1890).

⁸³ Mann, *J. Chem. Soc.*, 461 (1934).

⁸⁴ Van Alphen, *Rec. trav. chim.*, **55**, 412, 669, 835 (1936); **56**, 343, 529, 1007 (1937); **57**, 265 (1938), **58**, 544, 1105 (1939); **59**, 31 (1940).

diamines,⁸⁴ and a bromoalkyl alkylamine condensation,⁸⁵ have been studied but most of the emphasis has been placed on the lower-molecular-weight products which could be isolated. Polymeric quaternary ammonium salts have been obtained by the reaction of compounds of the type $\text{Br}(\text{CH}_2)_n\text{N}(\text{R})_2$, where $n = 3, 7, 8, 9$, and 10 .⁸⁶ These products were hygroscopic solids with molecular weights in the range of 1500 to 10,000, depending on the nature of R and the size of n . Some cyclic products were obtained when $n = 3$ and R was greater than methyl.

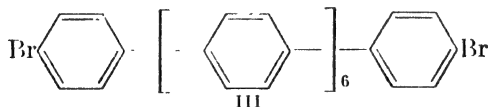
Zimmerman and Lochte⁸⁷ showed that the product of the reaction of diacetyl and hydrazine⁸⁸ is a linear polymer (II) with a molecular weight between 300 and 400. Other diketones and hydrazines gave similar linear polyazines.



Arvin⁸⁹ prepared polyether resins from phenolic bodies, polyhalides, and polyalcohols in an alkaline medium.

Previously, some work had been done on the formation of polyphenylene ethers by the oxidation of *o*-cresol,⁹⁰ but the products were only trimers. Also, Staudinger and Staiger⁹¹ have used the Ullmann reaction to get to the hexamer stage in the polyphenylene ether series and have made viscosity studies of these ethers.

Polymeric hydrocarbons have been prepared by the action of metals on dihalogen compounds. The work of Riese⁹² on the reaction between *p*-dibromobenzene and sodium was one of the earliest investigations in this field, but the nature of the polymeric products was not understood until Goldschmiedt⁹³ and later Jacobson⁹⁴ showed that the chief product of the reaction, $\text{C}_{48}\text{H}_{32}\text{Br}_2$, was probably a linear polymeric product having eight benzene nuclei (III). Jacobson also prepared a polymeric



⁸⁵ Cowan and Marvel, *J. Am. Chem. Soc.*, **58**, 2277 (1936).

⁸⁶ Gibbs, Littmann, and Marvel, *ibid.*, **55**, 753 (1933); Lehman, Thompson, and Marvel, *ibid.*, **55**, 1977 (1933); Gibbs and Marvel, *ibid.*, **56**, 725 (1934), **57**, 1137 (1935).

⁸⁷ Zimmerman and Lochte, *ibid.*, **58**, 948 (1936); **60**, 2456 (1938).

⁸⁸ Curtius and Thun, *J. prakt. Chem.*, [2] **44**, 175 (1891); Diels, *Ber.*, **35**, 350 (1902); Diels and Pflaumer, *Ber.*, **48**, 223 (1915).

⁸⁹ Arvin, U. S. patent, 2,060,715; 2,060,716 (1936).

⁹⁰ Goldschmidt, Schulz, and Bernard, *Ann.*, **478**, 1 (1930).

⁹¹ Staudinger and Staiger, *Ann.*, **517**, 67 (1935).

⁹² Riese, *Ann.*, **164**, 161 (1872).

⁹³ Goldschmiedt, *Monatsh.*, **7**, 40 (1886).

⁹⁴ Jacobson, *J. Am. Chem. Soc.*, **54**, 1513 (1932).

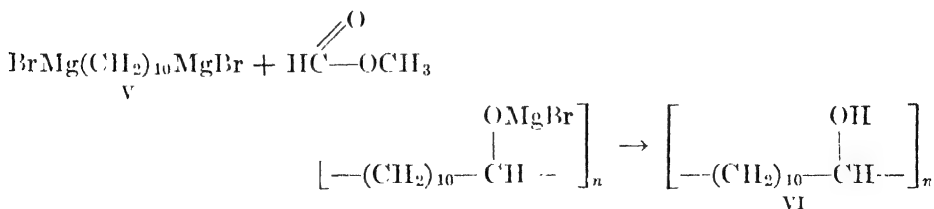
brominated hydrocarbon containing approximately 31 *p*-xylylene residues (IV) by the action of magnesium on *p*-xylylene dibromide.



The action of sodium on decamethylene bromide in ether gave a series of normal hydrocarbons from which $\text{C}_{50}\text{H}_{102}$, $\text{C}_{60}\text{H}_{122}$, and $\text{C}_{70}\text{H}_{142}$ were isolated by molecular distillation.⁹⁵ The residue contained still higher hydrocarbons, but they could not be distilled without decomposition. The data of Meyer⁹⁶ and Dunkel⁹⁷ show that the molecular cohesion of a C_{70} hydrocarbon is about 71,000 calories and that of a C_{80} hydrocarbon is about 81,000 calories. Since the heat of separation of a carbon-carbon bond is about 75,000 calories it would be expected that a C_{80} hydrocarbon would decompose rather than distill.⁹⁵

These hydrocarbons of high molecular weight were also used to carry out a rough check on one of the controversial subjects in polymer studies. It had been suggested⁹⁸ that the apparent decrease in the molecular weight of rubber and other polymers of very high molecular weight when heated gently or subjected to mechanical strain was real and was due to a thermal instability of these molecules at temperatures slightly above room temperature. The decrease in thermal stability from methane (decomposition temperature 650–700°)⁹⁹ to ethane (550–600°)¹⁰⁰ and ethane to hexadecane (*ca.* 470°),¹⁰¹ if followed on to higher members, would lead to such a result. However, a study of the thermal stability of triacontane, tetracontane, pentacontane, hexacontane, and heptacontane showed that the change from C_{30} up to C_{70} was so slight that it would be safe to say that a paraffin hydrocarbon of a molecular weight of even greater than 200,000 would be stable at room temperature.

Bifunctional Grignard reagents¹⁰² (V) have been treated with methyl formate to yield polymeric alcohols (VI).



⁹⁵ Carothers, Hill, Kirby, and Jacobson, *ibid.*, **52**, 5279 (1930).

⁹⁶ Meyer, *Naturwissenschaften*, **16**, 781 (1928).

⁹⁷ Dunkel, *Z. physik. Chem.*, **A138**, 42 (1928).

⁹⁸ Staudinger, *Ber.*, **59**, 3037 (1926).

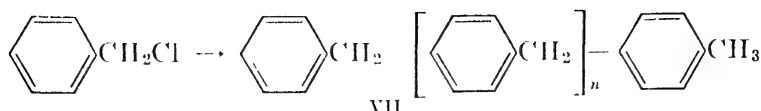
⁹⁹ Bone and Wheeler, *J. Chem. Soc.*, **81**, 542 (1902).

¹⁰⁰ Williams-Gardner, *Fuel*, **4**, 430 (1925).

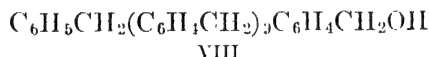
¹⁰¹ Gault and Hessel, *Ann. chim.*, [10] **2**, 319 (1924).

¹⁰² Carothers and Kirby, *J. Am. Chem. Soc.*, **54**, 1588 (1932).

The Friedel and Crafts reaction has also been used to produce polymeric materials. Thus, benzyl chloride reacts with traces of aluminum chloride to give complex soluble and insoluble products.¹⁰³ The soluble polymer is probably linear. The chlorine seems to be removed entirely by some side reaction.



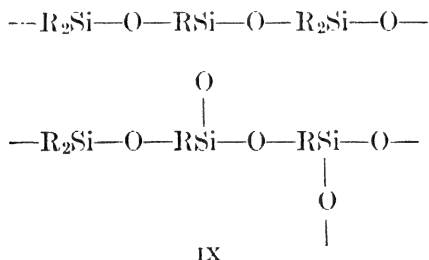
Shriner and Berger¹⁰⁴ have found that sulfuric acid converts benzyl alcohol to a mixture of at least two polymers, one of which has a composition identical with the soluble linear polymeric hydrocarbon reported by Jacobson¹⁰³ and the other has a terminal hydroxyl group (VIII).



Oxidation of these polymers to yield both *o*-phthalic and terephthalic acids shows that both *ortho* and *para* positions in the benzene nucleus are involved in polymer formation.

The polymeric alkyl silicon oxides are another interesting type of polymer. Kipping¹⁰⁵ first recognized that the silicanediols $\text{R}_2\text{Si}(\text{OH})_2$ condense intermolecularly to yield polymeric anhydrides and silicones. The silicanetriols, $\text{RSi}(\text{OH})_3$, likewise were known to condense to white, powdery "siliconic acids" $(\text{RSiOOH})_x$.¹⁰⁶

Rochow and Gilliam¹⁰⁷ have recently found that the silicanediols may be made to condense with the silicanetriols to yield solid polymers, probably of a cross-linked siloxane structure (IX).



¹⁰³ Jacobson, *ibid.*, **54**, 1513 (1932).

¹⁰⁴ Shriner and Berger, *J. Org. Chem.*, **6**, 305 (1941).

¹⁰⁵ Kipping, *J. Chem. Soc.*, **91**, 218 (1907); Robison and Kipping, *ibid.*, **93**, 439 (1908); **101**, 2142 (1912); Martin and Kipping, *ibid.*, **95**, 302 (1909); Kipping, *ibid.*, **101**, 2106 (1912).

¹⁰⁶ Meads and Kipping, *ibid.*, **105**, 679 (1914); **107**, 459 (1915); Ladenburg, *Ann.*, **164**, 300 (1872); **173**, 143 (1874).

¹⁰⁷ Rochow and Gilliam, *J. Am. Chem. Soc.*, **63**, 798 (1941).

The polymeric methyl silicon oxides (IX, $R = -CH_3$) are colorless, transparent, horny resins and are unique in their thermal stability, no perceptible change being produced by heating in air at 200° for a year. Hyde and DeLong¹⁰⁸ have also prepared silicon-containing polymers.

ADDITION POLYMERIZATION

Addition polymerization has no exact parallel in the reactions encountered in classical organic chemistry. An unsaturated molecule becomes activated, reacts with other unactivated molecules to produce long-chain compounds, and then in some way the reaction is stopped. Mark has aptly named these phases of the addition polymerization reaction initiation, propagation, and cessation.¹⁰⁹ This true addition polymerization reaction is not to be confused with the self-addition of one or two molecules of an unsaturated compound to produce dimers and trimers. In true polymerization these small units rarely are found in the reaction mixtures. Addition polymers usually range from 10,000 to 200,000 in molecular weight.

Strictly speaking, the addition polymers, like the condensation polymers, are not chemical individuals. They are mixtures of long-chain compounds made up of members of a *polyhomologous* series; that is, they have the same recurring unit and they are of practically the same order of molecular weight. The purity of the monomer is highly important if useful polymers are to be obtained.

In the chain reactions which produce the polymers, side reactions may occur such as branching and reaction with diluents and solvents. These side reactions are still little understood and will not be discussed in detail here. The actual mechanism of initiation, propagation, and cessation of these reactions can be treated more satisfactorily after a study of some of the facts which have been determined concerning various polymers.

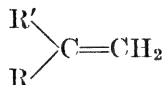
The various unsaturated monomeric types which polymerize by addition polymerization are the olefins and their derivatives, the dienes, the acetylenes, the aldehydes, and certain strained cyclic monomers which may be called pseudounsaturated. The olefins and the dienes are the most important technically and have received the greatest amount of study. In the field of addition polymerization Staudinger has done the greatest amount of work and has laid the foundation for much of the work which others have done.

¹⁰⁸ Hyde and DeLong, *ibid.*, **63**, 1194 (1941).

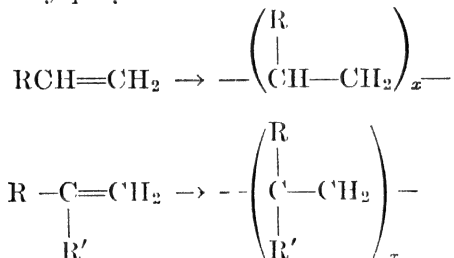
¹⁰⁹ Mark, "Physical Chemistry of High Polymeric Systems," Interscience Publishers New York (1940), p. 311.

Olefins and Their Derivatives

A wide variety of olefins has been polymerized by addition but the limitations are fairly definite and can be expressed with fair certainty. In the general molecule,



if R and R' are hydrogen or low-molecular-weight alkyl groups, the substances will usually polymerize.



Only when R and R' are both methyl groups has the polymerization of a disubstituted ethylene been extensively studied. Apparently, it is impossible to polymerize a symmetrically substituted olefin $\text{RCH}=\text{CHR}$ or a tri- or tetrasubstituted olefin to obtain high-molecular-weight products. This last limitation may be due to lack of present knowledge rather than to some intrinsic property of these molecules. Some tetrasubstituted halogen derivatives of ethylene have been polymerized.

If either R or R' or both are unsaturated or electron-attracting groups, such as phenyl, carbonyl-containing residues, $-\text{OCOR}$, chlorine, or cyano, polymerization usually is more readily accomplished than in the case of the simple olefins. If, however, R is phenyl, R' must be hydrogen or the polymerization is very difficult to accomplish. Styrenes with substitution on the vinyl residue polymerize to low-molecular-weight molecules.¹¹⁰

Copolymerization, in which two different olefins or olefin derivatives take part in the chain reaction, is quite complex. Cases of this sort will be considered after the simpler ones have been described. It may be well, however, to point out at this time that there are olefin derivatives of the type $\text{RCH}=\text{CHR}$ which will not themselves polymerize but which do enter into copolymerization reactions with other polymerizable olefin derivatives. Thus, ethyl maleate and maleic anhydride can be

¹¹⁰ Staudinger and Breusch, *Ber.*, **62**, 442 (1929).

combined with vinyl chloride to give copolymers but will not themselves readily polymerize.

The chain polymerization reaction is usually started by a catalyst such as a metal halide, a metalloid halide, or a peroxide. Boron fluoride and aluminum chloride work best at low temperatures. Benzoyl peroxide and hydrogen peroxide are common peroxide-type catalysts. Polymerization may also be induced by heating and by irradiation with ultra-violet light. Oxygen also plays an important role in polymerization processes of this type, possibly through the formation of olefin peroxides.

Staudinger¹¹¹ has shown that the temperature and general conditions under which styrene is polymerized have a marked effect on the molecular weight of the polymer. This is shown by the facts summarized in Table I. In general these results carry over to other addition-poly-

TABLE I
MOLECULAR SIZE OF POLYSTYRENE AS AFFECTED BY
METHOD OF POLYMERIZATION

| METHOD OF POLYMERIZATION | APPEARANCE OF POLYMER | AVERAGE MOLECULAR WEIGHT | SINTERING POINT | SOLUBILITY IN ETHER |
|------------------------------------|----------------------------|--------------------------------|--------------------|------------------------|
| Heating with SnCl_4 | White pulverulent material | 3,000 | 105–110° | Soluble |
| Under nitrogen at 150° | White powder | 23,000 | 120–130 | Slightly soluble |
| Under nitrogen at 100° | White fibers | 120,000 | 160–180 | Insoluble |
| In air at room temperature | White fibers | 200,000 | 180 | Insoluble |
| Under nitrogen at room temperature | White fibers | 600,000 | 180 | Insoluble |

merization reactions. Low-temperature polymerizations with little catalyst are likely to produce the highest-molecular-weight polymers.

Staudinger¹¹¹ has introduced the term degree of polymerization to indicate the number of recurring units in an addition polymer. In the case of styrene where the monomer has a molecular weight of approximately 100, the degree of the polymer is about $1/100$ of the molecular weight. The low-molecular-weight addition polymers with a degree number up to about 100 are called hemicolloids by Staudinger.¹¹¹ They behave much like ordinary low-molecular-weight compounds as regards

¹¹¹ Staudinger, "Die hochmolekularen organischen Verbindungen," J. Springer, Berlin (1932).

solubility, viscosity of solutions, etc. Those polymers with a degree above 100 and below 1000 are called mesocolloids. They constitute a transition group, and the physical properties change more or less gradually from those of low-molecular-weight substances to those of very-high-molecular-weight substances. Polymers with a degree above 1000 are called eucolloids. They usually swell markedly with solvents and dissolve only very slowly to give solutions which show abnormal viscosity behavior. In these solutions the individual molecules which are dissolved begin to approach the size of the ordinary colloidal particle. As mentioned earlier, three-dimensional polymers are invariably insoluble even when of relatively low molecular weight. Slightly cross-linked polymers of the linear type usually swell with solvents.

The older method of producing polymers from the olefins and their derivatives was to use the pure liquid or a solution in an organic solvent in which the catalyst would dissolve. This method is still widely followed, but industrially some of these reactions are now carried out in emulsion. The monomeric material is suspended in water or a water-organic solvent mixture and the catalyst and an emulsifying agent are added. The polymer may separate as it forms or it may remain in emulsion and be coagulated at the end of the polymerization. The use of the emulsion technique has greatly improved the homogeneity of some of the polymeric products which are technically available.

Ethylene. As long ago as 1797 experiments involving the polymerization of ethylene were being described in the scientific literature;¹¹² therefore no attempt will be made to give a bibliography covering all the succeeding work. Thermal polymerization of ethylene in the presence of metal chloride catalysts¹¹³ at about 70 atmospheres was found to produce butane and other lower paraffins, together with olefinic and naphthenic oils. Burk, Baldwin, and Whitacre¹¹⁴ have made a very careful study of the dimerization of ethylene in glass at 625°. The main idea behind the earlier work seemed to be the production of gasoline or lubricating oil from ethylene. Summaries of these phases of ethylene polymerization are available.¹¹⁵

Most of the earlier work on the polymerization of ethylene did not lead to a true chain polymerization with the production of large molecules. In recent years this has been achieved by heating ethylene at pressures above 1000 atmospheres and temperatures from 100° to 400°

¹¹² Deiman, Troostwyk, Lauweenburg, and Bondt, *Ann. chim.*, **21**, 58 (1797); *Ann. Physik*, **2**, 208 (1799).

¹¹³ Ipatieff and Rutala, *Ber.*, **46**, 1748 (1913); *J. Russ. Phys. Chem. Soc.*, **45**, 995 (1913).

¹¹⁴ Burk, Baldwin, and Whitacre, *Ind. Eng. Chem.*, **29**, 326 (1937).

¹¹⁵ Egloff, Schaad, and Lowry, *J. Phys. Chem.*, **35**, 1825 (1931); Sullivan, Voorhees Neeley, and Shankland, *Ind. Eng. Chem.*, **23**, 604 (1931).

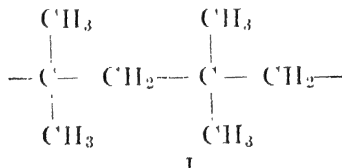
with a carefully controlled amount of oxygen.¹¹⁶ This produces a solid



polymer which is tough and waxy to the touch and melts around 118°. The mean molecular weight estimated by viscosity measurements in a tetrahydronaphthalene solution runs from 2000 up to 20,000, depending on the temperature and pressure of polymerization. These polymers show a crystalline structure by x-ray diffraction methods. The product has been produced technically in England under the name "Polythene."

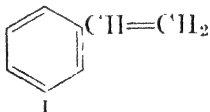
Isobutylene. Isobutylene, which is available by petroleum-cracking processes, can be converted to a mixture of dimers, trimers, and tetramers by acid treatment, but this process is hardly a true polymerization. By use of metal halide catalysts, isobutylene has been converted to polymeric materials having a molecular weight of 25,000 to 400,000 or even higher.¹¹⁷ These polymers have been studied and their useful properties described in a series of publications.¹¹⁸

These polyisobutenes are long carbon chains having *gem*-methyl groups on alternate carbon atoms (I). The products with molecular



weights up to about 27,000 are thick liquids. The higher polymers are white, tough, elastic solids with properties which make them useful rubber substitutes. They cannot be vulcanized, however. The saturated nature of the polyisobutylene renders it inert; hence it is practically unaffected by ozone, strong acids, and similar agents which destroy rubber.

Styrene. Styrene or phenylethylene (I) was first isolated in 1831 by the distillation of storax, and in 1839 Simon, a Berlin apothecary,



¹¹⁶ Fawcett, Gibson, and Perlin, U. S. patent, 2,153,553 (1939).

¹¹⁷ Otto and Mueller-Cunradi, U. S. patent, 2,130,507 (1938).

¹¹⁸ Thomas, Zimmer, Turner, Rosen, and Frolich, *Ind. Eng. Chem.*, **32**, 299 (1940); Sparks, Lightbown, Turner, Frolich, and Klebsattel, *ibid.*, **32**, 731 (1940); Thomas, Sparks, Frolich, Otto, and Mueller-Cunradi, *J. Am. Chem. Soc.*, **62**, 276 (1940); Thomas, Lightbown, Sparks, Frolich, and Murphree, *Ind. Eng. Chem.*, **32**, 1283 (1940).

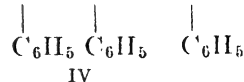
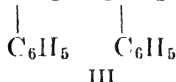
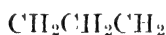
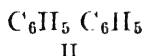
called attention¹¹⁹ to the fact that it gave polymeric products. The early literature is full of references to the changes which styrene undergoes under the influence of heat, light, and various chemical agents. However, the work of Staudinger¹²⁰ and his collaborators has shown the real usefulness of polystyrene. Much of our knowledge of other addition polymers has come from this work on styrene.

Thermal polymerization of styrene at moderate temperatures (150–175°) leads to a water-white, transparent polymer which has a superficial resemblance to glass. It is much softer than glass and is tough rather than brittle. It can be cut, shaved, machined, and molded under pressure and heat. It displays a rubberlike elasticity when warmed. The polymer is soluble in aromatic hydrocarbons and many esters.

When the polymerization is carried out at too high a temperature a more brittle and less soluble product is produced. This product has less shock resistance and a lower transverse tensile strength than the polymer produced at moderate temperatures.

Styrene may be polymerized to give polymers of very high molecular weight (p. 741), and the nature of the catalyst, the temperature, the solvent, etc., affect the nature of the polymer. It is generally believed that the activated molecules react by a chain mechanism with unactivated molecules to build up the long-chain polymer. Hence, if many active centers are formed, the unactivated monomer will be divided between all of them and the chain length of the polymer will not be great. With fewer active centers and slower growth of polymer chains the very-high-molecular-weight products result. Staudinger and Frost¹²¹ made some of the first kinetic studies on polymerization by following the rate of change of styrene to polystyrene by bromine titration.

Considerable work on the structure of polystyrene has appeared. Staudinger and Steinhofer¹²² used pyrolytic methods to degrade polystyrene and isolated such products as 2,4-diphenyl-1-butene (II), 1,3-diphenylpropane (III), 2,4,6-triphenyl-1-hexene (IV), 1,3,5-triphenyl-



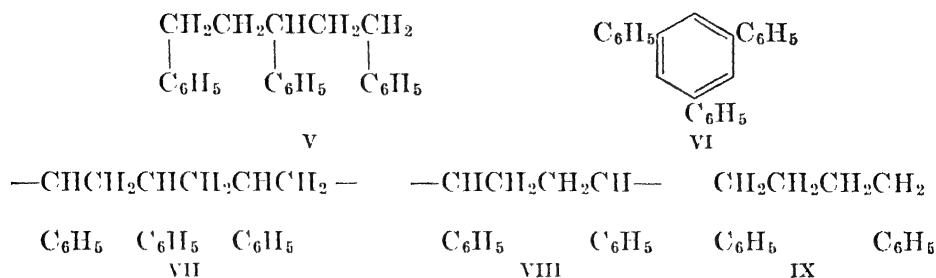
pentane (V), and 1,3,5-triphenylbenzene (VI), all of which are consistent with the notion that polystyrene is a long chain of molecules having phenyl groups on alternate carbon atoms (VII).

¹¹⁹ Simon, *Ann.*, **31**, 265 (1839).

¹²⁰ Staudinger, Brunner, Frey, Garbsch, Signer, and Wehrli, *Ber.*, **62**, 241 (1929).

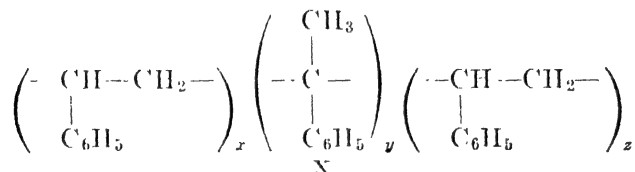
¹²¹ Staudinger and Frost, *Ber.*, **68**, 2351 (1935).

¹²² Staudinger and Steinhofer, *Ann.*, **517**, 35 (1935).

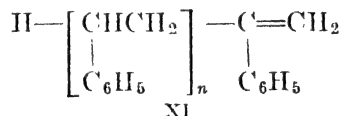


Midgley, Henne, and Leicester¹²³ have isolated 1,4-diphenylbutane (IX) by the action of sodium and alcohol on styrene and have accordingly suggested structure VIII for the recurring unit in polystyrenes. It seems unlikely, however, that such a "head-to-head, tail-to-tail" type of structure could yield the pyrolytic products which have been characterized.¹²²

Very recently it has been suggested¹²⁴ that polystyrene chains have some methyl side chains (X). This means that some shift of hydrogen has occurred during the polymerization.



Staudinger has suggested that the end groups on a polystyrene molecule are hydrogen and an unsaturated group. The double bond is very difficult to detect, and, though these end groups seem reasonable,



they must be regarded as tentative. Attempts to label the end groups by carrying out the polymerization in the presence of substances such as sulfuric acid, acetic acid, acetic anhydride, and methanol¹²² have not helped settle the problem.

There is evidence¹²⁵ that a large polystyrene molecule may increase in molecular weight when placed in fresh monomeric styrene under the proper conditions. This would indicate a terminal double bond, which could either be reactivated to combine with more styrene or could be

¹²³ Midgley, Henne, and Leicester, *J. Am. Chem. Soc.*, **58**, 1961 (1936).

¹²⁴ Kropa and Barnes, 101st Meeting of the American Chemical Society, St. Louis, Missouri, April, 1941.

¹²⁵ Houtz and Adkins, *J. Am. Chem. Soc.*, **55**, 1609 (1933).

captured by new growing chains of polystyrene, thus giving rather complex branched structures. Such branched structures have marked effects on viscosity.

Thermal polymerization of styrene may also be carried out in solution. The general effect is a slowing down of the reaction and a decrease in the degree of the polymer.¹²⁶ The exact nature of the change, however, seems to vary with the solvent. Extended studies of the effects have been carried out by Suess¹²⁷ and by Schulz.¹²⁸

Carbon tetrachloride shows a decided ability to depress the average degree of the polymer.¹²⁷ It may be that the role of this solvent is more than that of a simple diluent, inasmuch as it has been reported that polystyrenes prepared in carbon tetrachloride are halogen-containing, and that the amount of chlorine is roughly that required for one carbon tetrachloride per polystyrene molecule.¹²⁹ Benzene and toluene, on the other hand, seem to depress the degree much less effectively than the other solvents.

The properties of the polystyrene molecule are dependent not only on its chemical nature but also on the size and shape of the molecule. It has been suggested that at least in solution the molecule takes the form of a long rod. Such solutions are apparently true solutions in that the polystyrene is molecularly dispersed in a solvated form. The eucolloidal solutions, for example, show no change in viscosity on long standing or shaking or after operations such as successive dilutions and concentrations.¹³⁰ It is quite possible, however, to degrade the molecules in solution and hence lower the viscosity. Thermal treatments, if prolonged, and especially if carried out at moderate temperatures, result in a molecular degradation.¹³¹ Mechanical treatments will accomplish the same end. Polystyrene solutions agitated in a ball mill show a continuous decrease in molecular weight with increasing duration of treatment. Forcing tetralin solutions through a platinum orifice under conditions leading to a high degree of turbulent streaming also decreases the molecular weight.¹³² It is possible that the rodlike shape of the molecule contributes to the ease of shear of the structure.

If a polymerization of styrene is carried out in an emulsion of sodium

¹²⁶ Breitenbach and Rudorfer, *Monatsh.*, **70**, 37 (1937); Jorde, *ibid.*, **70**, 193 (1937).

¹²⁷ (a) Suess, Pilch, and Rudorfer, *Z. physik. Chem.*, **A179**, 361 (1937); *Oesterr. Chem.-Ztg.*, **40**, 287 (1937); (b) Suess and Springer, *Z. physik. Chem.*, **A181**, 81 (1937).

¹²⁸ (a) Schulz and Husemann, *Z. physik. Chem.*, **B36**, 184 (1937); (b) Schulz, Dinglinger, and Husemann, *ibid.*, **B43**, 385 (1939).

¹²⁹ Breitenbach, Springer, and Abrahameczik, *Oesterr. Chem.-Ztg.*, **41**, 182 (1938); Breitenbach and Maschin, *Z. physik. Chem.*, **A187**, 175 (1940).

¹³⁰ Staudinger and Frey, *Ber.*, **62**, 2909 (1929).

¹³¹ Staudinger, Frey, Garbsch, and Wehli, *Ber.*, **62**, 2912 (1929).

¹³² Staudinger and Heuer, *Ber.*, **67**, 1159 (1934).

oleate the result is a latexlike suspension in which the molecules appear to be spherical, since Einstein's viscosity law, based on the assumption of a spherical form, is obeyed. The polymer may be precipitated, however, just as rubber is obtained from latex, and after drying and dissolving in benzene the usual abnormal viscosity, characteristic of a rod shape, appears.¹³³ This demonstrates the influence of the medium on the nature of the molecular shape.

The assumption that the molecules are essentially rodlike in nature forms the basis for Staudinger's relation between the viscosity of such solutions and the molecular weight of the dissolved material:

$$M = \frac{1}{K_m} \times \frac{\eta_{sp}}{C_{gm}}$$

in which M is the molecular weight, K_m a constant, η_{sp} the specific viscosity, and C_{gm} the concentration of polymer expressed in terms of the concentration of the monomer in moles per liter. This relation may also be expressed in terms of the degree of polymerization in which P is

$$P = \frac{1}{K_m} \times \frac{\eta_{sp}}{C}$$

the number of monomeric units in the polymer and C is the concentration of the polymer in grams per liter.

Both these relations are valid if the proper value for K_m is chosen. The problem is complicated because any molecular-weight value must of necessity be an average value, and because there are very few methods of estimating molecular weights in this range. However, the utility of Staudinger's viscosity method has been confirmed in practice, especially with polystyrenes. Schulz has demonstrated that the osmotic-pressure method may also be adapted to yield molecular-weight values.¹³⁴ To obtain significant values it is necessary to use a polymer fraction of a reasonably narrow molecular-weight range. These values are in accordance with the results obtained through the use of the ultracentrifuge^{135, 1316} and may then be used for the determination of the value of the constant in Staudinger's formula.¹³⁶ This constant is then useful over neighboring ranges of molecular weights.

Occasionally some difficulty is encountered in the use of viscosity methods. The molecular weights become abnormal, especially under certain circumstances, such as high-temperature polymerizations. This

¹³³ Staudinger and Husemann, *Ber.*, **68**, 1691 (1935).

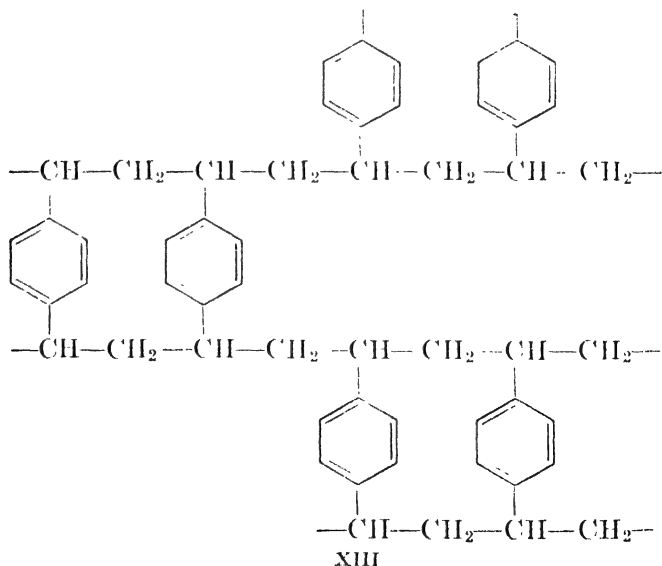
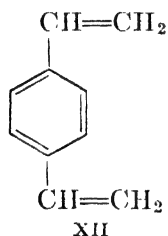
¹³⁴ (a) Staudinger and Schulz, *Ber.*, **68**, 2320 (1935); (b) Schulz, *Z. physik. Chem.*, **A176**, 317 (1936).

¹³⁵ Signet, *Trans. Faraday Soc.*, **32**, 296 (1936).

¹³⁶ Schulz and Dinglinger, *Z. physik. Chem.*, **B43**, 47 (1939).

may be due to the introduction of a small degree of branching in the molecular structure. It has been suggested^{134a} that this is due to an infrequent activation in the *para* position, with consequent chain branching. It is also possible that the branching occurs in the fashion previously noted; that is, that a large styrene molecule is incorporated in a growing chain through its terminal double bond. In thermal polymerization an increase in temperature increases the gross rate of reaction and decreases the chain length of the molecule, and both these effects contribute to an increase in the concentration of double bonds at any particular time during the polymerization. This, coupled with the general activating influence of a temperature rise, may explain the observed effects. A confirmation of the existence of some ramification in polystyrene molecules has been obtained by Signer¹³⁷ from studies of the streaming double refraction of polystyrene solutions.

The introduction of cross-linking into the molecule leads gradually to polymeric products with decreased solubilities. It was observed in some of the earlier work on polystyrenes that some preparations from industrial styrene were harder and less soluble than others. Investigations of the starting materials revealed the presence of small amounts of divinylbenzene (XII) in the styrene. Divinylbenzene itself is capable of polymerization¹³⁸ to form a structure such as that illustrated by formula XIII. As would be expected from this type of structure, the molecule presents a three-dimensional aspect and is hard and insoluble.

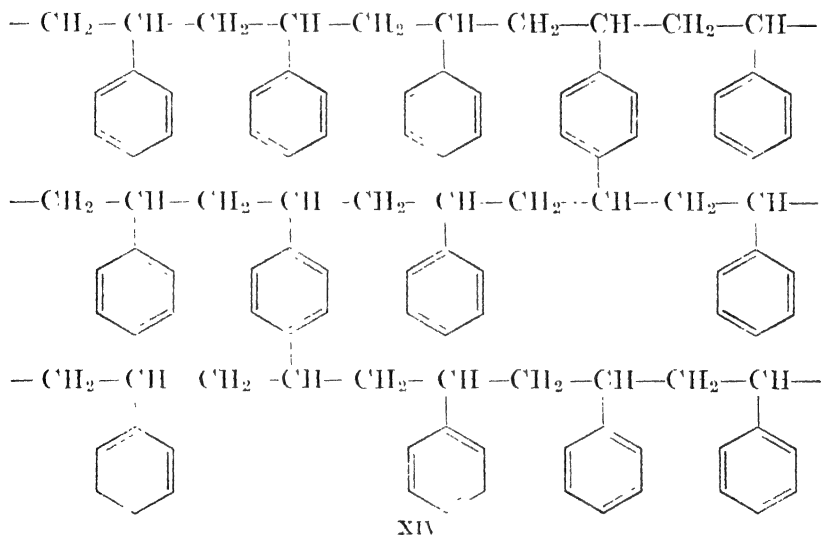


¹³⁷ Signer, *Helv. Chim. Acta*, **19**, 897 (1936).

¹³⁸ Lespieau and Deluchat, *Compt. rend.*, **190**, 683 (1930).

It was found that the introduction of as little as 0.01 per cent of divinylbenzene in styrene affected the character of the resulting polymer.¹³⁹ It became, of course, harder and less soluble. An increase in the divinylbenzene content to about 0.1 per cent resulted in a product which still swelled on contact with solvents such as benzene, but which was almost completely insoluble. With more than 1 per cent of divinylbenzene, the polymer was a hard glass, impervious to solvents.

The insoluble polystyrene is very similar in appearance to the ordinary soluble styrene polymer, and is of the same general chemical structure, except that the linear polystyrene molecules are bound together at more or less infrequent intervals by divinylbenzene units. This is illustrated in XIV:



The effects occasioned by varying the relative amounts of the two molecular species have been investigated by Staudinger.¹⁴⁰ Only a very small concentration of divinylbenzene is sufficient to bring about a non-swelling condition, but as this concentration is lowered the polymer gradually takes on a swelling character and becomes partially soluble. With still lower amounts of divinylbenzene, in the neighborhood of 0.0025 per cent or less, the polymer becomes soluble, but the viscosity of such solutions is abnormally high. For example, a 0.0025 per cent divinylbenzene polymer obtained at 100° displayed an η_{sp}/C value of 41.6, as compared with the value 21.5, taken under the same conditions,

¹³⁹ Staudinger and Heuer, *Ber.*, **67**, 1164 (1934); Staudinger and Husemann, *Ber.*, **68**, 1618 (1935).

¹⁴⁰ Staudinger, Heuer, and Husemann, *Trans. Faraday Soc.*, **32**, 323 (1936).

for a polystyrene also obtained at 100°. In general, although no fixed relation exists, increasing the chain length of the polystyrene molecule decreases the amount of divinylbenzene required for inducing swelling without solution.

It has been found that, varying with the conditions, one molecule of divinylbenzene for every 10,000-50,000 molecules of styrene is sufficient to induce a marked effect. This corresponds to less than one molecule of divinylbenzene to every polystyrene molecule, so that something besides a purely integral valence bonding is effective in preventing solution. Observations of solubility phenomena displayed by polystyrenes of the very low-divinylbenzene-content variety show that they are slowly attacked by the solvent, and that very gradually a sort of extraction takes place and some linear polystyrenes of the normal type find their way into solution. It is apparent, therefore, that some sort of "netting effect" is present; possibly the cross-linked molecules are intertwined with some of the linear molecules and hence hold them fast.

Compounds fitting the character of divinylbenzene in this particular instance have been referred to generally as netting agents. Obviously, they must contain at least two double bonds capable of incorporation into the chain. In an extended investigation involving styrene and a number of other monomers, Norrish and Brookman¹⁴¹ have found a number of such agents, which in decreasing order of effectiveness are divinylacetylene, divinylsulfide, divinylsulfone, and hexatriene. Those which are relatively ineffective are divinylether, divinylsulfoxide, diallyl, and isoprene. Many other examples of such compounds and their applications are appearing in the patent literature.

Acrylic Acid Derivatives. Acrylic acid was discovered in 1843,¹⁴² and the properties of its polymer were described in 1872.¹⁴³ The α -methylacrylic acid derivatives were discovered in 1865,¹⁴⁴ and the fact that they would polymerize was recognized by Fittig and Paul in 1877.¹⁴⁵ The technical development in this field apparently dates back to the researches of Otto Röhm.¹⁴⁶ Methyl methacrylate polymers have been in commercial production in the United States since about 1937.

The large-scale manufacture of the acrylate polymers is based on cheap production of the monomeric esters. The reaction between

¹⁴¹ Norrish and Brookman, *Proc. Roy. Soc. (London)*, **A163**, 205 (1937).

¹⁴² Redtenbacher, *Ann.*, **47**, 113 (1843).

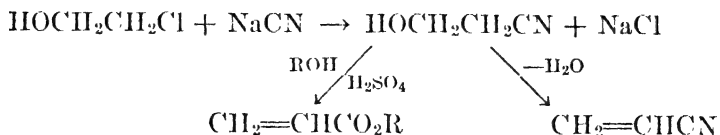
¹⁴³ Linnemann, *Ann.*, **163**, 369 (1872).

¹⁴⁴ Frankland and Duppa, *Ann.*, **136**, 12 (1865).

¹⁴⁵ Fittig and Paul, *Ann.*, **188**, 52 (1877).

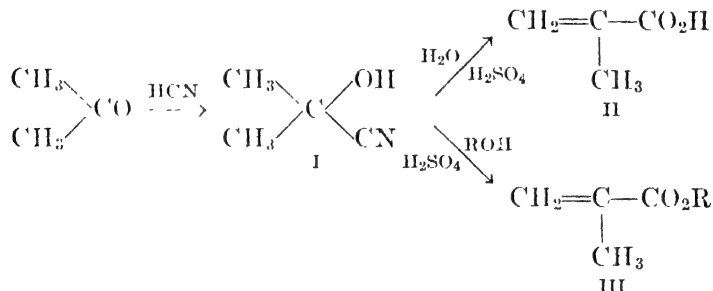
¹⁴⁶ O. Röhm, "Über Polymerization Produkte der Akrylsäure," Dissertation, Tübingen (1901); v. Pechmann and Röhm, *Ber.*, **34**, 427 (1901); Röhm, *Ber.*, **34**, 573 (1901); Röhm, German patent, 262,707 (1912); U. S. patent, 1,121,134 (1914); German patent, 295,340 (1915).

ethylene chlorohydrin and sodium cyanide¹⁴⁷ gives β -hydroxypropio-

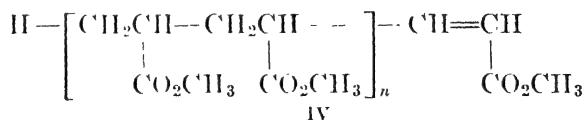


nitrile, which on dehydration yields acrylonitrile, $\text{CH}_2=\text{CHCN}$; on dehydration, hydrolysis, and esterification yields the alkyl acrylates, $\text{CH}_2=\text{CHCO}_2\text{R}$; and on dehydration and hydrolysis yields acrylic acid, $\text{CH}_2=\text{CHCO}_2\text{H}$.

α -Methacrylic acid (II) is produced from acetone through the cyanohydrin (I). By treatment of the cyanohydrin with an alcohol and sulfuric acid it is possible to go directly to the alkyl α -methacrylate (III).¹⁴⁸ The methyl ester, commonly called methyl methacrylate, is the most important ester of this type.



The acrylates and methacrylates are readily polymerized under the influence of heat, light, or peroxides.¹⁴⁹ Benzoyl peroxide is one of the most common of the catalysts. Oxygen will catalyze the polymerization although an excess of oxygen acts as an inhibitor. The acrylate polymers (IV) are apparently long carbon chains with ester groups on alternate carbon atoms. In the methacrylates (V) the methyl substituent is also on the carbon atom carrying the ester group. The end groups may be hydrogen and an olefin residue although this is not definitely established. Recent work on the kinetics of these polymerization reactions indicates that one end group may come from the peroxide used as a catalyst (p. 775).

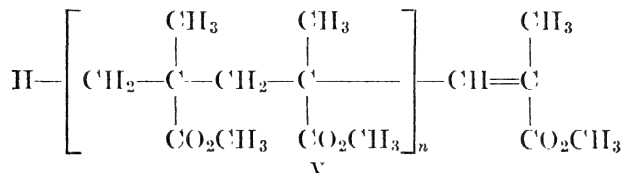


¹⁴⁷ Röhm and Haas A.-G., German patents, 365,350 (1919); 571,123 (1928); Bauer U. S. patents, 1,388,016 (1921), 1,829,208 (1931).

¹⁴⁸ Imperial Chemical Industries, Ltd., British patents, 405,699 (1934); 419,457 (1934)

¹⁴⁹ Röhm and Haas A.-G., British patent, 304,681 (1930).

In keeping with this structure (V), polymethyl methacrylate may be degraded by heat to dimeric and trimeric products.¹⁵⁰ Polymethyl



acrylate can be hydrolyzed with alkali to give the salt of a polymeric acid; it reacts with methylmagnesium iodide to give a polyalcohol; on heating with ammonia it yields amides and imides. Polymethyl methacrylate does not undergo these transformations because of steric hindrance.

The polymers vary in molecular weight, depending on the conditions under which they are prepared, but the commercial products are in the neighborhood of 40,000. The polyesters are insoluble in water, alcohol, and aliphatic hydrocarbons. Ethers act as swelling agents rather than as solvents. Aromatic hydrocarbons, ketones, esters, chloroform, *sym*-tetrachloroethane, and some other active hydrogen compounds are good solvents. Polyacrylic acid is slowly soluble in water. Its alkali salts are readily water-soluble. Polyacrylonitrile is highly insoluble in all common solvents. This is probably because of a cross-linked structure due to hydrogen bonding between the active methylene hydrogen of one chain and the nitrile group of another. It has been shown that a 1,3-dicyanide such as trimethylene cyanide is highly associated¹⁵¹ by such forces.

The methyl methacrylate polymers are marketed under such trade names as "Plexiglas," "Crystalite," and "Lucite." The products are light in weight, tough, and elastic. They have good optical transparency, are stable to light, and are permanently thermoplastic. The sheet material is widely used in airplane manufacture. The powdered material is used for molding toilet articles, lenses, furniture, etc.

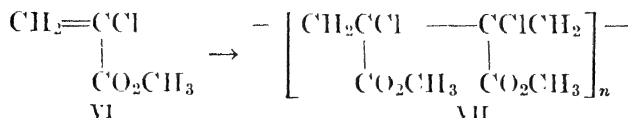
Some patents¹⁵² have been granted for modified acrylate polymers which are harder and hence more suitable for the manufacture of spectacle lenses. This hardening is achieved by the addition of agents which cause some cross-linking. Methacrylic anhydride and ethylene methacrylate are types of reagents which have been suggested. These obviously act like divinylbenzene when mixed with styrene.

¹⁵⁰ Staudinger and Urech, *Helv. Chim. Acta*, **12**, 1107 (1929); Staudinger and Kohlschütter, *Ber.*, **64**, 2091 (1931); Staudinger and Trommsdorff, *Ann.*, **502**, 201 (1933).

¹⁵¹ Copley, Zellhoefer, and Marvel, *J. Am. Chem. Soc.*, **62**, 227 (1940).

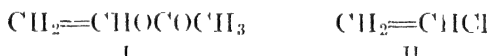
¹⁵² Hill, British patent, 423,790 (1935); Kistler and Barnes, U. S. patents, 2,189,733 and 2,189,735 (1940).

The alkyl α -haloacrylates (VI) are of theoretical interest since they apparently give polymers (VII) which have the units arranged in a

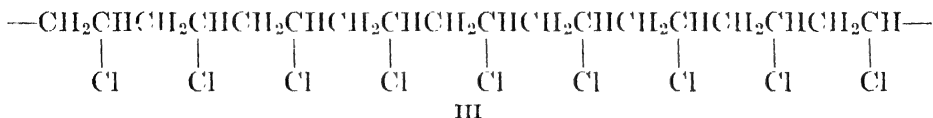


head-to-head, tail-to-tail fashion rather than head-to-tail, as is the common arrangement of monomer units in a polymer chain. The fact that these polymers have halogens on adjacent carbon atoms is shown by their liberating iodine from solutions of potassium iodide in peroxide-free dioxane solution.¹⁵³ Other reactions and physical properties corroborate this evidence for the unusual arrangement of monomer units in the polymer chain of the α -haloacrylates.

Vinyl Esters. Vinyl acetate (I) and vinyl chloride (II) are the most important of the vinyl esters which readily yield polymeric products.



Both are readily available from acetylene by the addition of acetic acid and hydrogen chloride, respectively. Baumann¹⁵⁴ and Ostromysslenskii¹⁵⁵ did the early work on polyvinyl halides. Staudinger and his students¹⁵⁶ described many of the chemical properties of the polyvinyl halides and concluded that these polymers had halogen on alternate carbon atoms along the carbon chain (III). This view of the structure was confirmed by a study of the reaction between zinc and an extremely dilute solution of polyvinyl chloride in dioxane.¹⁵⁷ Under these conditions of high dilution zinc removes chlorine atoms from the polyvinyl chloride molecule until about 84-87 per cent of the chlorine content has been removed. The remaining polymer is soluble, indicating that no cross-linking has accompanied the removal of chlorine. Flory has calculated¹⁵⁸ that 86.47 per cent of the chlorine would be removed from a polyvinyl chloride having halogen in the 1,3-positions (III) if the



^{15b} Marvel and Cowan, *J. Am. Chem. Soc.*, **61**, 3156 (1939).

¹⁵⁴ Baumann, *Ann.*, **163**, 308 (1872).

¹⁵⁵ Ostromysslenskii, *J. Russ. Phys. Chem. Soc.*, **44**, 204, 240 (1912).

¹⁵⁶ Staudinger, Brunner, and Feisst, *Helv. Chim. Acta*, **13**, 805 (1930).

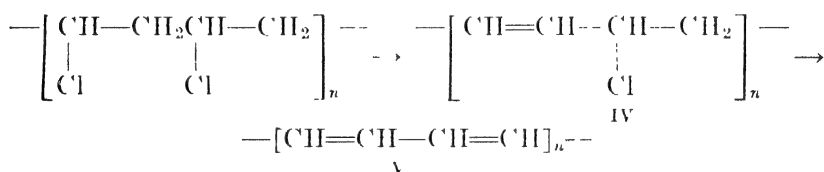
¹⁵⁷ Marvel, Sample, and Roy, *J. Am. Chem. Soc.*, **61**, 3241 (1939).

¹⁵⁸ Flory, *ibid.*, **61**, 1518 (1939). See also Wall, *ibid.*, **62**, 803 (1940), and Simha *ibid.*, **63**, 1479 (1941).

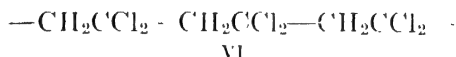
removal follows statistical laws. The fact that not all the halogen is removed is due to isolation of chlorine atoms between reacting pairs. Similar statistical calculations lead to the conclusion that only 81.60 per cent of the chlorine should be removable by the zinc reaction in a perfectly random arrangement of vinyl chloride units in the polymer chain. Hence, the evidence available indicates that all the vinyl chloride units in the polymer chain are arranged in a head-to-tail fashion.

Commercial polyvinyl chloride is a high-melting, rather insoluble polymer. It can be softened by the addition of triereryl phosphate,¹⁵⁹ and the polymer thus plasticized, sold under the trade name of "Koro-seal," finds many uses as a substitute for rubber.

Polyvinyl chloride has a tendency to darken on exposure to sunlight, and this has been attributed to the loss of hydrogen chloride. This seems to be a sound explanation of the formation of color. It will be noted that loss of one hydrogen chloride molecule will make the adjacent chlorine an allyl chloride (IV), which will be even more likely to react again than will an isolated chlorine atom. Hence, polyene chains (V) which are highly colored will be set up whenever hydrogen chloride is lost. Certain stabilizers are used technically to avoid these reactions.



Polyvinylidene chloride (VI) was first systematically studied by Staudinger and Feisst¹⁶⁰ and the structure established as a head-to-tail



polymer. The product is now in commercial production in this country and is marketed under the trade name of "Saran."

Polyvinyl acetate has been studied by several investigators. Herrmann¹⁶¹ and Staudinger¹⁶² were among the first to describe accurately

¹⁵⁹ Brous and Semon, *Ind. Eng. Chem.*, **27**, 667 (1935); Schoenfeld, Browne, and Brous, *ibid.*, **31**, 964 (1939).

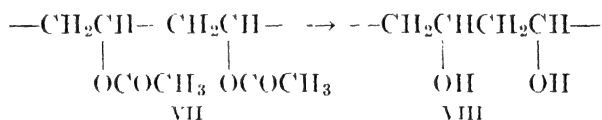
¹⁶⁰ Staudinger and Feisst, *Helv. Chim. Acta*, **13**, 832 (1930).

¹⁶¹ Herrmann and Haehnel, *Ber.*, **60**, 1658 (1927).

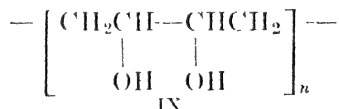
¹⁶² Staudinger, Frey, and Starck, *Ber.*, **60**, 1782 (1927); Staudinger and Schwalbach *Ann.*, **488**, 8 (1931); Staudinger, *Ber.*, **59**, 3019 (1926)

the reactions and properties of this polymer. The ordinary polymer has a molecular weight of approximately 20,000 although samples with a molecular weight of 80,000 have been obtained. The polymer is clear and colorless, and softens at 30–40°. It possesses good stability to light and heat, but its low softening point prevents its successful use as a molding compound. It is very soluble in alcohols, ketones, esters, and even aromatic hydrocarbons and halogenated aliphatic hydrocarbons. When the polymerization is carried out in the presence of chloroform, the polymer contains chlorine.

Hydrolysis of polyvinyl acetate (VII) can be readily accomplished to give water-soluble polyvinyl alcohol, (VIII).

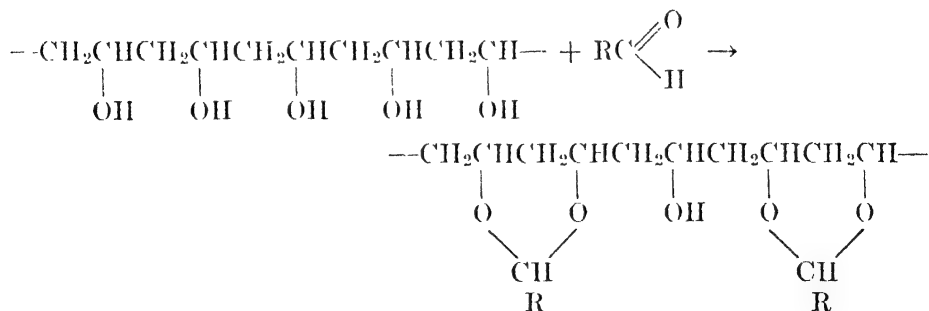


Staudinger¹⁶² recognized the usefulness of this reaction in his work on structure proof. He reported that oxidation of polyvinyl alcohol with nitric acid gave oxalic and succinic acids. This indicates the possibility of some head-to-head, tail-to-tail groups (IX) in polyvinyl



alcohol and hence also in polyvinyl acetate. A more recent study of polyvinyl alcohol¹⁶³ showed that no 1,2-glycol structure was present since the polymer could not be oxidized by periodic acid, which is a specific oxidizing agent for this structural unit.¹⁶⁴

Polyvinyl alcohol has been used to make oil-resistant tubing. Its principal application is in the manufacture of the acetals (X), which

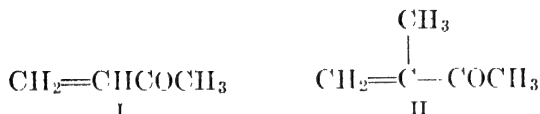


¹⁶³ Marvel and Denoon, *J. Am. Chem. Soc.*, **60**, 1045 (1938).

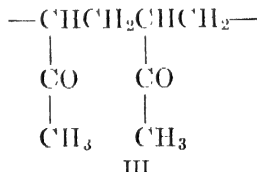
¹⁶⁴ Malaprade, *Compt. rend.*, **186**, 382 (1928); *Bull. soc. chim.*, [5] **1**, 833 (1934); Fleury and Fatome, *J. pharm. chim.*, [8] **21**, 247 (1935); Karier and Hirohata, *Helv. Chim. Acta*, **16**, 959 (1933); Jackson and Hudson, *J. Am. Chem. Soc.*, **59**, 2049 (1937).

serve as the inner layer for safety glass. In the process of acetal formation some of the hydroxyl groups become isolated just as chlorine atoms are isolated in the zinc dehalogenation of polyvinyl chloride.¹⁵⁸ These acetal resins are resistant to water, have excellent light resistance, adhere to glass, and have a high degree of elasticity.

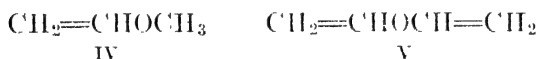
Miscellaneous Vinyl Polymers. Methyl vinyl ketone (I) and methyl isopropylidene ketone (II) polymerize readily and have been under



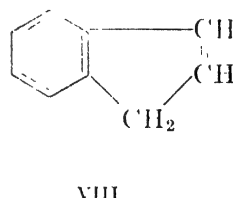
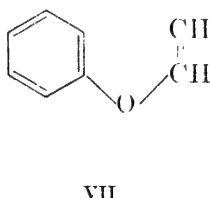
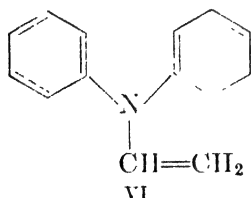
consideration as industrial plastics. The polymer of methyl vinyl ketone has been shown to have a head-to-tail or 1,5-diketone structure (III).¹⁶⁵



Vinyl ether (IV) and divinyl ether (V) have been used to some extent but mainly as constituents of copolymers (p. 757). Vinylcarbazole¹⁶⁶



(VI) has been patented, as have many other arylated vinyl types. The coumarone (VII) and indene (VIII) polymers have received consider-



able study and have attained some practical importance.¹⁶⁷

¹⁶⁵ Marvel and Levesque, *J. Am. Chem. Soc.*, **60**, 280 (1938); **61**, 3234 (1939).

¹⁶⁶ Reppe and Keyssner, German patent, 618,120 (1934).

¹⁶⁷ Stobbe and Faiber, *Ber.*, **57**, 1838 (1924); Whitby and Katz, *J. Am. Chem. Soc.*, **50**, 1160 (1928); Risi and Gauvin, *Can. J. Research*, **13B**, 228 (1935); Bergmann and Taubadel, *Ber.*, **65B**, 463 (1932); Sheehan, Kelly and Carmody, *Ind. Eng. Chem.*, **29**, 576 (1937); Carmody, Sheehan, and Kelly, *ibid.*, **30**, 245 (1938); Carmody, *ibid.*, **32**, 525 (1940).

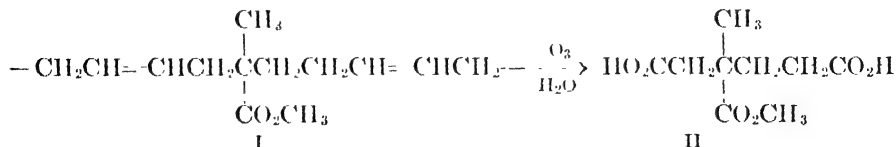
Copolymers

When two different vinyl derivatives are mixed in the monomeric state and then polymerized, there is often produced a mixture of copolymers which contain both the monomeric units in simple chains. The technical development in this field is far ahead of the scientific literature. Not every pair of vinyl monomers can be converted to a copolymer, and there are some monomeric ethylenic derivatives which will enter into copolymers but will not themselves polymerize.

Perhaps the best-known group of copolymers are the "Vinylites," which contain different ratios of vinyl chloride and vinyl acetate. It is an interesting fact that vinyl acetate alone polymerizes more rapidly than vinyl chloride; however, when the two monomers are mixed and then polymerization is effected, the polymer first formed is richer in vinyl chloride than is the mixture of monomers from which the polymer is formed.¹⁶⁸ Since the two monomers do not enter the polymer chain at the same rate, there probably is a difference in composition in each polymer chain that is laid down due to the change in concentration of the monomers in the unpolymerized fraction. This fact is not stated specifically in the literature, but a hint of it is given in a patent,¹⁶⁹ by the suggestion that more uniform copolymers can be obtained by adding one component gradually to the polymerizing mixture.

Styrene and maleic anhydride form a heteropolymer.^{4, 170} The most readily produced polymer contains one styrene unit for each maleic anhydride unit arranged in a systematic fashion. A polymer containing more than one molecule of styrene for each molecule of maleic anhydride can be produced, but it is not certain that this is not a mixture of polystyrene and the copolymer with a 1:1 ratio of the monomer.

A study has been made of the copolymers of methyl methacrylate and butadiene¹⁷¹ prepared from equivalent quantities of the monomers by the emulsion technique. Ozonization of the polymer (I) gave the monomethyl ester of a tribasic acid (II) in about 50 per cent yields.



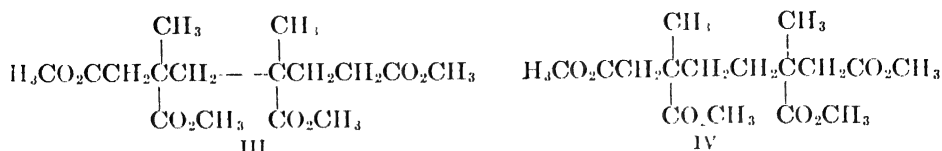
¹⁶⁸ Staudinger and Schneiders, *Ann.*, **541**, 151 (1939); Marvel and Jones, unpublished data; see Wall, *J. Am. Chem. Soc.*, **63**, 821, 1862 (1941).

¹⁶⁹ Fikentscher and Hengstenberg, U. S. patent, 2,100,900 (1937).

¹⁷⁰ Voss and Diekhäuser, U. S. patent, 2,047,398 (1936); Hopff, *Kunststoffe*, **28**, 289 (1938).

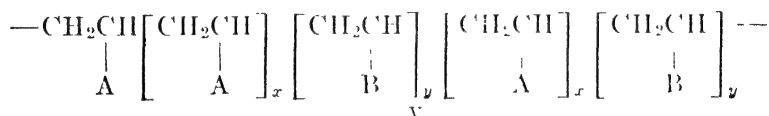
¹⁷¹ Hill, Lewis, and Simonsen, *Trans. Faraday Soc.*, **35**, 1067, 1073 (1939).

This proved that this copolymer is mainly made up of the two monomers occurring alternately in the chain. Some dimethyl ester of a tetrabasic acid was also formed and isolated as the tetramethyl ester (III or IV).



While the exact structure of this tetrabasic acid was not determined, the isolation of a product of this composition shows that some of the monomeric units are joined in an irregular fashion, as seems to be true for the "Vinylites."

Melville¹⁷² has described the preparation of some interesting copolymers. A vessel was filled with the vapor of a polymerizable monomer and irradiated to start polymerization. When the polymerization was well under way, as indicated by a pressure drop, the monomer was removed by evacuation and a new gaseous monomer added. The polymerization continued at once, and presumably the new monomer became a part of the same polymer chain started by the first monomer. By changing from one monomer to another several times, Melville believed he had molecules such as shown below (V).



No study of the properties of these "molecular sandwiches" has yet been made.

This section on copolymers is of necessity incomplete, as most of the work in this field has been done in the technical laboratories and published only in patents. Hence, it is difficult to locate and evaluate the available information.

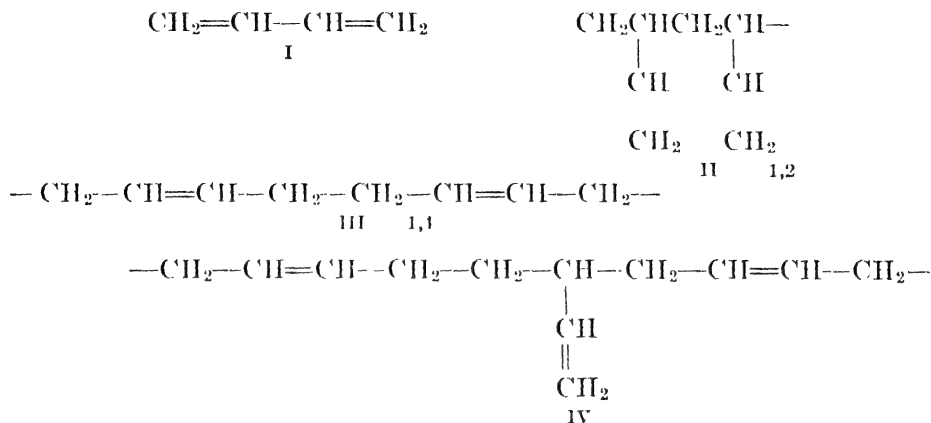
Dienes

The polymerization of a conjugated diene (I) is a special case of addition polymerization. Two possible reactions may be involved in the formation of the polymer, 1,2-addition (II) or 1,4-addition (III). In nature the diene polymer, rubber, has the units arranged regularly head-to-tail and 1,4.¹⁷³ When an attempt is made to polymerize but-

¹⁷² Melville, *Trans. Inst. Rubber Ind.*, **15**, 209 (1939).

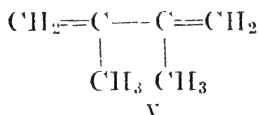
¹⁷³ Pummerer, *Kautschuk*, **10**, 149 (1934); *Rubber Chem. Tech.*, **8**, 39 (1935).

adiene in the laboratory, the product appears to be made up of some 1,2-unions and many 1,4-unions in the same chain (IV). In a sense this



is related to copolymerization, and the numbers of 1,2- and 1,4-recurring units are determined by the rates of the two polymerization reactions. There is also the complicating reaction of cross-linking, which occurs by a new addition polymerization reaction in which the side-chain vinyl groups participate.

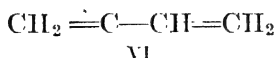
Synthetic Rubber. The investigations in the diene field have been very extensive because of the search for a cheap synthetic rubber. The amount of research which has been done has been closely connected with general economic and political conditions throughout the world. Thus, the shortage of natural rubber in Germany in 1914-1918 led to the development of the production of a synthetic rubber from dimethylbutadiene (V) at the rate of about 150 tons a month at one time. When natural rubber became available again this synthetic product was abandoned.



With the increase in the price of crude rubber which began in 1925 and lasted long enough to impress many industrial chemical corporations and their associates with the value of a good synthetic rubber, a renewed interest in the problem developed. The price of rubber then declined, however, and only a few companies continued extensive research programs. Rubber continued to drop in price, reaching very low levels in 1932-1933 (less than \$0.05 per pound for ribbed smoked sheets), and then advanced again slowly. In June, 1940, the price of ribbed smoked sheets was about \$0.22-0.23 per pound. During this time the

du Pont Company was engaged in the process for producing "Duprene," later called "Neoprene," from chloroprene or 2-chlorobutadiene (VI).

Cl



The resulting product was rather costly, especially at first (*ca.* \$1.00 per pound in 1935-1936), but fortunately it is greatly superior to natural rubber in some respects, especially in its resistance to the action of hydrocarbon solvents. It has therefore found continuous use and the price has dropped to lower levels.

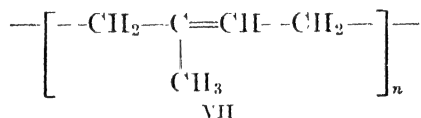
In Germany a great deal of interest has been shown in the rubber problem over the last ten years, as evidenced by the number of patent applications and the present development of the industry in that country. Synthetic rubbers have been in production for some time. These were originally prepared from butadiene (I) by the action of sodium and were known as "Buna" rubbers. Lately several new modifications, such as "Buna N" and "Buna S," have appeared. These are outstanding improvements and are copolymers of butadiene with acrylonitrile and styrene, respectively.

Other important synthetic rubbers which have appeared recently in this country are "Ameripol," "Butyl Rubber," "Koroseal," "Chemi-gum," "Hy-Car," polyisobutylene, and "Thiokol." Ameripol, Hy-Car, Chemi-gum, and Butyl Rubber have not been described in detail in the literature, but they are probably copolymers of which one constituent is butadiene. Koroseal, Thiokol, and polyisobutylene have been described in earlier sections.

All these materials have slightly different characteristics which influence their use, but all have the same objective: the replacement of natural rubber as a major commodity. It seems likely that the future development in this field will not be directed to the production of a single material which will serve as a substitute for natural rubber in all its manifold uses, but rather that a number of different polymers of a wide range of properties will be manufactured, and that within any particular field there will be available a product which is better or cheaper than natural rubber. The tire industry, of course, serves as the largest rubber consumer in all industrial countries (the consumption in this country is estimated at about two-thirds of the total rubber importation) and hence will be the scene of the greatest competition. The whole field is not a small one; rubber consumption in the United States for the month of May, 1940, was estimated at 51,619 long tons. One of the

most fruitful of research avenues seems to be the study of copolymerization, although the mode of processing plays such an important role that studies of the polymerization proper and the technical utilization of the preliminary product are inseparable.

It will be noticed that a rather curious event has occurred in the course of the development of synthetic rubbers. Unvulcanized natural rubber is an isoprene polymer (VII) and as such consists of a hydro-



carbon chain containing about one double bond for every five carbon atoms. It was therefore thought, very naturally, that rubberlike properties were dependent on exactly this type of structure, and that only a diene polymer would approach natural rubber in its qualities. But it now appears that something besides the diene polymer structure is concerned with these properties, since the substitutes polyisobutylene, Koroseal, and Thiokol are not derived from dienes. The length of the molecule is undoubtedly of great importance.

Another factor must be considered in these studies. Rubber as precipitated from latex is very different in its properties from the tough elastic material which is usually the desired form. Vulcanization and the incorporation of certain materials such as zinc oxide and carbon black are corollaries to the development of the finished product. The changes in structure which occur during the vulcanization procedure are generally taken to be the creation of cross-links between the molecules by means of sulfur bridges set up at the unsaturated bonds. This means that some variety of cross-linking seems to be necessary for the full development of a good rubber, and that for a normal vulcanization some unsaturation must be present.

The arrangement of the molecules also seems to be highly important. It is apparently essential that the linear molecules of the polymer be aligned in the same fashion, side by side, for the full development of elastic properties. In rubber this is carried out by natural forces. In the synthetic materials a sort of mechanical vulcanization may often be observed. Suitable working of the polymer leads to an alignment of the molecules and consequently to elasticity.

All the industries using large quantities of rubber as a raw material have been continuously engaged in research directed to the production of better and more useful articles. The design of the finished product and the technological features of its manufacture are of necessity based

on the assumption that natural rubber will be the starting point, and consequently they must take full cognizance of the strength and weaknesses of rubber. The new materials may surpass rubber in many respects and yet be inferior in others, or at least possess some different qualities, so that much technological research will be required if full advantage is to be taken of these synthetic materials.

The question of finished cost, balanced against the ability of the product to do the work for which it was designed, must play an important part in the scheme of development. Easy production of a monomer in the laboratory does not guarantee its success in a commercial field. Any attempt to produce a synthetic rubber must be accompanied by a method of producing the monomer at a low cost. For a long while this phase of the situation caused considerable difficulty. At the present time the new methods developed by the petroleum industry seem able to supply the starting materials at low cost and in tremendous volume. Butadiene and isobutylene may be produced easily, as may acetylene, which is the starting point for chloroprene. It therefore seems probable that within a few years synthetic rubber will be fairly inexpensive.

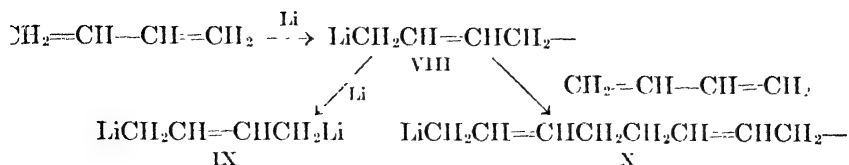
Polymerization of dienes by means of the alkali metals, especially sodium, is a well-known method. The use of sodium in this connection was noted¹⁷⁴ as early as 1910 in England. This reaction has been investigated extensively both academically and commercially. Ziegler¹⁷⁵ has been especially identified with the study of alkali metals and alkali alkyls and their effect on dienes. This work was reviewed in 1936.¹⁷⁶ It has been found that both 1,2- and 1,4-addition may occur, but that higher temperatures favor 1,4-addition. It is presumed that the alkali metal or alkali alkyl adds to the double bond to form an intermediate compound and that then this intermediate of the 1,4- or 1,2-type adds butadiene molecules stepwise. Lithium is especially useful for these studies. The alkali metal takes a position at the end of the chain after each addition and is then available for another addition. Schulz¹⁷⁷ has pointed out that some of Ziegler's conditions are not those which would obtain in a true polymerization reaction and that a slightly different interpretation is possible. With butadiene, for example, lithium may add at one of the double bonds:

¹⁷⁴ Matthews and Strange, British patent, 21,790 (1910).

¹⁷⁵ Ziegler and Bahr, *Ber.*, **61**, 253 (1928); Ziegler, Grossmann, Kleiner, and Schafer, *Ann.*, **473**, 1 (1929); Ziegler and Kleiner, *Ann.*, **473**, 57 (1929); Ziegler, Dersch, and Wollthan, *Ann.*, **511**, 13 (1934); Ziegler, Jakob, Wollthan, and Wenz, *Ann.*, **511**, 64 (1934); Ziegler, Grimm, and Willer, *Ann.*, **542**, 90 (1940).

¹⁷⁶ Ziegler, *Angew. Chem.*, **49**, 499 (1936).

¹⁷⁷ Schulz, *Ergeb. exakt. Naturw.*, **17**, 367 (1938). See also Houwink "Chemie und Technologie der Kunststoffe," Akad. Verlags. Leipzig (1939).



The next reaction will be dependent on the relative concentrations of lithium and butadiene. If the lithium is present in large amounts, then IX will be formed in considerable amount. The intermediate VIII may also add butadiene to form X, which is then faced with the same alternatives as the original compound (VIII). The lithium is therefore both a chain initiator and a chain terminator, and the lower the concentration of the monomer, the lower will be the average molecular weight of the product. The final products, however, will be the same whether the reaction proceeds chainwise through a free radical mechanism or through a metal-alkyl addition of successive monomer units as suggested by Ziegler.

That only comparatively small amounts of sodium are necessary for the polymerization has been a general observation. For example, an experiment utilizing only 0.001–0.3 per cent sodium has been described.¹⁷⁸ The sodium and butadiene are condensed together on a cold surface to obtain a fine dispersion of the sodium. Solid polymers may be obtained in two to thirty-six hours at 10–15°.

The kinetics of the reaction have been studied by Abkin and Medvedev¹⁷⁹ for butadiene and sodium. These authors hold Ziegler's view that two atoms of sodium add to butadiene, and that subsequent addition of butadiene occurs with the sodium atom continually moving to the chain end to provide an active center. It was found that a primary period was observed during which the rate of polymerization gradually increased until some definite value was reached, after which it became constant. This preliminary period is presumably due to the formation of primary sodium-butadiene compounds, and is very much slower than the rate of addition of butadiene to these active points. A number of experimental difficulties were encountered during the course of the investigation, and it was found that the results were reproducible only when carefully purified butadiene was employed in the absence of oxygen and light.

For commercial polymerizations sodium has been employed in the form of wire or rods and in a finely divided state as powder. Zinc rods

¹⁷⁸ Zelmanov and Shalnikov, *J. Phys. Chem. (U.S.S.R.)*, **4**, 353 (1933). See Bolland, *Proc. Roy. Soc. (London)*, **A178**, 24 (1941), for a recent discussion of the mechanism of diene polymerization by metal catalysts.

¹⁷⁹ Abkin and Medvedev, *Trans. Faraday Soc.*, **32**, 286 (1936).

dipped in sodium have also been used. An atmosphere of carbon dioxide was employed with the process for the production of "Methyl Rubber B" by the Badische Anilin und Soda-Fabrik. At the present time sodium polymerizates are still in commercial use. "Buna 85" of the I. G. Farbenindustrie A.-G., as well as "Buna 115," are sodium-butadiene polymers. The Russian products "SK A" and "SK B" and the Polish "Ker" are also of the same type. The German rubbers are liquid-phase polymerizates prepared with finely divided sodium.¹⁷⁷ Chloroprene cannot be polymerized by this method.

Much of the synthetic rubber in commercial production today is polymerized in emulsion. The resulting latex is easy to handle, and the products are generally superior to those obtained in other fashions. Lower temperatures may be employed, and consequently the amount of low-molecular-weight polymers is decreased. The monomer is emulsified in an aqueous solution with some agent as sodium oleate, linoleate, or stearate, or the sodium salt of certain sulfonic acids. The mixture is usually homogenized to increase the yield and the velocity of polymerization. A protective colloid as gelatin, milk, albumin, glue, or a similar compound is often added. A catalyst containing loosely held oxygen is generally necessary to initiate the reaction, and compounds such as hydrogen peroxide, benzoyl peroxide, perborates, persulfates, percarbonates, ozonides, and metallic peroxides have been used. The organic or inorganic salts of metals such as cobalt, manganese, and lead have also been suggested. Certain halogen compounds such as trichloroacetic acid and carbon tetrachloride have been said to have an accelerating effect on the polymerization.

Most of the current rubbers being made in Germany are copolymers.¹⁸⁰ "Buna S5" is now produced only in small quantity since its soft vulcanizates are considerably weaker than those of natural rubber or the copolymers. It has some advantage for use as a hard rubber. The principal mixed polymers employ styrene or acrylonitrile. "Buna S" is a styrene-butadiene copolymer prepared in aqueous emulsion. It is used generally for tires and mechanical rubber goods. Here a high degree of oil resistance is not demanded. In heat and abrasion resistance, it is said to be superior to natural rubber. It shows lower water absorption and has aging properties superior to those of natural rubber, but its resistance to hydrocarbon solvents represents only a very slight improvement. A hot-air plasticizing treatment at 110-140° is usually carried out on Buna S before vulcanization. A slight pressure is favorable. The process softens the product and allows further processing in the same fashion as natural rubber. Oxygen is apparently necessary for

¹⁸⁰ Koch, *Ind. Eng. Chem.*, **32**, 464 (1940).

this treatment, which seems to be an exothermic reaction, but no change in composition of the polymer has been detected.

"Perbunan" ("Buna N") and "Perbunan Extra" are prepared in an emulsion using butadiene and up to 40 per cent acrylonitrile. (The Extra grade contains more of the nitrile than the standard.) This polymer is not given a hot-air plasticizing treatment but is milled on cold rolls before processing. Its principal value lies in its resistance to hydrocarbon solvents, although it has been reported that excellent tires have been made from Buna N type polymers. The raw Perbunans are insoluble in gasoline and aliphatic hydrocarbons but are soluble in aromatic and chlorinated hydrocarbons and, unlike natural rubber and Buna S, in ketones such as acetone and methyl ethyl ketone. The vulcanized products are quite insoluble. Vulcanization of these materials is generally very similar to that of natural rubber.

Chloroprene is also polymerized in an emulsion. The normal speed of polymerization of chloroprene is much more rapid than that of isoprene, and apparently in emulsion form the rate is accelerated. Oxygen also acts as an accelerator. The outstanding properties of the finished product are its resistance to combustion (because of the high chlorine content) and, most important, its resistance to swelling when in contact with organic liquids. It is also more resistant to oxidants than is vulcanized natural rubber.

The development of the whole synthetic rubber field up to 1933 has been covered in an excellent fashion with great detail by Whitby and Katz.¹⁸¹ The situation to 1939 is reviewed by Konrad in Houwink's book.¹⁷⁷

Polysulfones

The addition of sulfur dioxide to an olefin or olefin derivative is a special case of copolymerization and is also a case of heteropolymerization since sulfur dioxide alone does not polymerize. The reaction was discovered by Solonina,¹⁸² who described the addition products of this type from allyl alcohol and various allyl ethers. Matthews and Elder¹⁸³ extended the reactions to the simple olefins from ethylene through amylene and showed that the products had the composition $(RCH=CH_2 \cdot SO_2)_n$.

The field was investigated very actively beginning about 1934 when several investigators in various laboratories simultaneously took up a study of these products. Staudinger in 1932¹¹¹ and Seyer and King¹⁸⁴ in

¹⁸¹ Whitby and Katz, *ibid.*, **25**, 1204, 1338 (1933).

¹⁸² Solonina, *J. Russ. Phys. Chem. Soc.*, **19**, 306, Note 1 (1887); *ibid.*, **30**, 826 (1898).

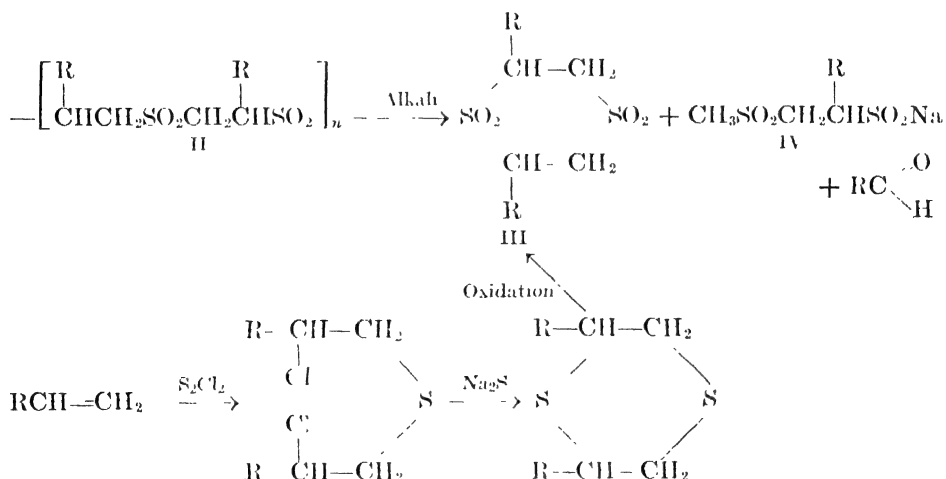
¹⁸³ Matthews and Elder, British patent, 11,635 (1914).

¹⁸⁴ Seyer and King, *J. Am. Chem. Soc.*, **55**, 3140 (1933).

$$\text{---}(\text{C}'\text{H}_2\text{C}'\text{H}_2\text{SO}_2)_n\text{---}$$

I

The polysulfones all have the head-to-head, tail-to-tail structure (II)¹⁸⁹ as shown by the alkaline cleavage to the cyclic disulfone (III) and



¹⁸⁹ Hunt and Marvel, *J. Am. Chem. Soc.*, **57**, 1691 (1935). See also reference 187.

carbon units, as only in propylene polysulfone is there evidence of an acid group in the molecule. Most of the polymers are alcohols, as they can be acylated with trichloroacetyl chloride. Hence the chain reaction apparently stops by the addition of the elements of water at the ends of the polymer chain.

A large number of substances have been found to act as catalysts for the polymerization reaction. In addition to oxygen, peroxides, and actinic light, which usually cause addition polymerization reactions, it has been reported¹⁹⁰ that nitrates, oxides of nitrogen, silver salts, and monovalent copper will catalyze polysulfone formation. Kharasch and Sternfeld¹⁹¹ have found that hydrogen chloride increases the activity of ascaridole as a catalyst and have been able to convert a trisubstituted olefin, 2-methyl-2-butene, to a polysulfone by this method.

The polysulfones are white, amorphous powders with relatively high melting points. They decompose at high temperatures to yield the original olefins or olefin derivatives and sulfur dioxide.¹⁸⁶ They are cleaved by alkalis to yield cyclic disulfones and other low-molecular-weight products.

These polymers have rather high molecular weights, which usually fall in the range of 50,000 to 200,000 on the basis of end-group analysis and viscosity of solutions.¹⁸⁷ They are soluble in various organic solvents if prepared from olefins with more than five carbon atoms.

Aldehydes

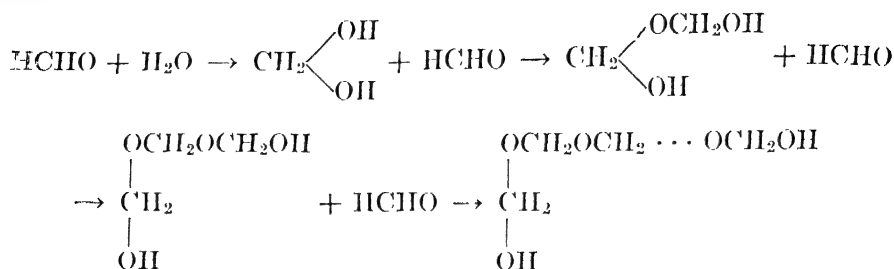
Aldehydes may polymerize to high-molecular-weight products in a number of fashions. The aldol condensation, for example, may be repeated successively with consequent formation of long-chain compounds. Formaldehyde may condense with itself to form the so-called formaldehyde sugars. The production of the polyoxymethylenes is, however, a different type of polymerization. The properties of these latter materials have been studied extensively by Staudinger.¹¹¹

Evaporation of an aqueous solution of formaldehyde results in the formation of paraformaldehyde. This is a fairly low-molecular-weight polymer, of degree probably up to about 50. A polymer of the same type, but of somewhat higher degree, may be obtained by the addition of sulfuric acid. There are three possibilities for the mechanism of the polymerization.

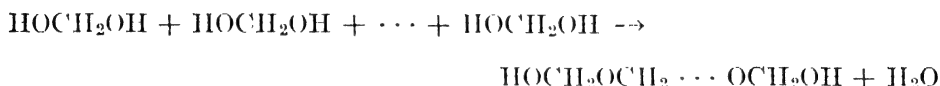
1. The condensation of formaldehyde molecules with a methylene glycol structure may occur as follows.

¹⁹⁰ Fitch and Frey, U. S. patent, 2,113,584 (1938), U. S. patent, 2,192,466 (1940).

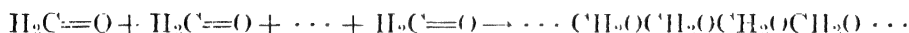
¹⁹¹ Kharasch and Sternfeld, *J. Am. Chem. Soc.*, **62**, 2559 (1940).



2. The condensation may proceed through a successive series of condensations of methylene glycol.

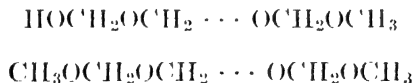


3. The polymerization may proceed through the carbonyl bond, probably with the addition of water to satisfy the end groups.

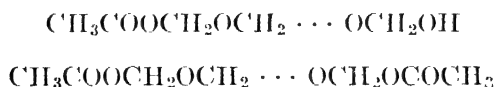


The latter mode of polymerization seems attractive as an explanation for the very-long-chain polyoxymethylenes produced from liquid formaldehyde at low temperatures (-80° , -20°). These substances are generally glassy solids which become plastic when heated and can be drawn into fibers. The fibers lack the elasticity of the polyester and polyamide fibers, but the possibility of their formation seems to indicate a high molecular weight. There is probably no difference in chemical structure between the higher polyoxymethylenes and the lower paraformaldehydes. Sauter¹⁹² has described the molecular structure to be inferred from molecular diffraction patterns.

In the lower ranges several modified structures may exist. If methanol is present in the aqueous solution, the polyoxymethylene may have one or both end groups present as methoxyl instead of the dihydrate structure.



These compounds contain up to about 100 oxymethylene units. Acetate end groups may also be introduced by acetylation.

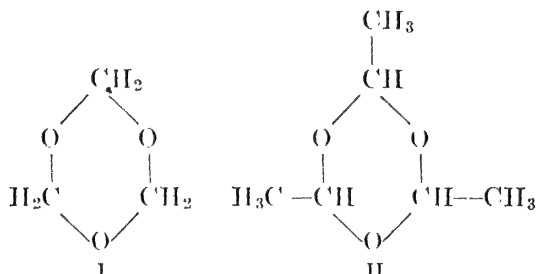


¹⁹² Sauter, *Z. physik. Chem.*, **B21**, 161, 186 (1933).

The dihydrate represents a hemiacetal structure and hence may be hydrolyzed by dilute acid or dilute alkali. The dimethyl ether is an acetal and is therefore stable to alkali, but may be hydrolyzed by acid. The diacetate may be decomposed by warm alkali and by dilute acid.

As these compounds are of relatively low molecular weight, end-group studies may be used for molecular-weight determinations. Hydrolysis of the dimethyl ether with dilute hydrochloric acid, for example, liberates methanol which may be determined analytically.

There also exists a compound, α -trioxymethylene, which is apparently a trimer (I). An analogous compound is also presumed to exist for acetaldehyde (II). Mixed compounds of this variety from two



moles of an aldehyde and one mole of chloral have been described by Hilbert.¹⁹³ Thioformaldehyde polymerizes very rapidly when prepared and is believed to assume a linear thiomethylene structure analogous to the polyoxymethylenes.

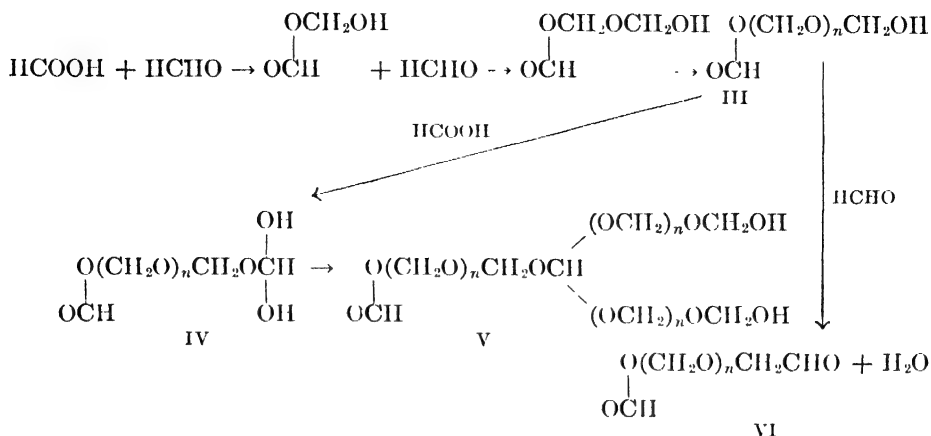
The polymerization of formaldehyde and acetaldehyde in the gaseous phase has been studied¹⁹¹ and it was found that formic acid had a marked accelerating effect. The mechanism is presumed to be the following: a formic acid molecule condenses with a formaldehyde molecule leading to an intermediate which may then add formaldehyde successively to form a long-chain compound (III). It may also add formic acid at any point and form an intermediate having two available hydroxyl groups (IV), both of which are capable of initiating polyoxymethylene chains. Hence the formic acid has the effect not only of initiating chains but also of causing them to branch (V). The reaction probably stops when a formaldehyde molecule reacts with a hydroxyl group at the end of a chain with loss of water (VI).

The higher aliphatic aldehydes undergo a very curious polymerization under high pressures.¹⁹⁵ *n*-Butyraldehyde, *n*-valeraldehyde, and

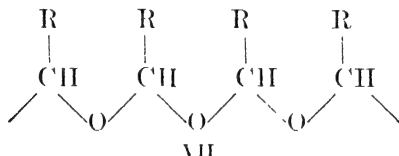
¹⁹³ Hibbert, Gillespie, and Montonna, *J. Am. Chem. Soc.*, **50**, 1950 (1928).

¹⁹⁴ Carruthers and Norrish, *Trans. Faraday Soc.*, **32**, 195 (1936).

¹⁹⁵ Conant and Peterson, *J. Am. Chem. Soc.*, **54**, 628 (1932).



n-heptaldehyde are transformed into hard, transparent solids by long treatment at 12,000 atmospheres. At 4000 to 6000 atmospheres with a benzoyl peroxide catalyst the product is white. Oxygen or peroxides act as catalysts for the reaction. The product is probably of the structure indicated by formula VII.



The nature of the end groups is uncertain. The butyraldehyde polymer is insoluble in the common solvents but swells in benzene and toluene. Depolymerization may be effected by heating or by small amounts of aqueous acids or alkalis.

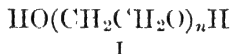
Numerous other observations have been made on aldehyde polymerizations. Glyoxal, for example, forms a polymer. Butyraldehyde on treatment with a little sodium hydroxide forms a series of higher-boiling products. Benzaldehyde under the influence of light forms resinous materials of the same elementary composition as the starting material. The structures of these materials, however, are uncertain.

Cyclic Compounds

The polymerization of cyclic compounds has been encountered previously in the polyesters (p. 707). Some lactones polymerize more or less readily to form long-chain polyesters. It is not certain whether a small amount of water intervenes to give the hydroxy acid, followed by successive addition of lactone rings, or whether the chain is built

up by simple coalescence of the rings. In any event, the stability of the lactone determines the rate of the polymerization.

The cyclic compounds ethylene oxide, ethylene sulfide, and ethylene imine polymerize rather easily. Ethylene oxide has been studied by Staudinger¹¹¹ and particularly by Hibbert.¹⁹⁶ Its polymerization is catalyzed by a number of materials, including stannic chloride, sodium, and trimethylamine. The reaction may proceed so rapidly as to become explosive. The structure of the resulting polymer is that shown by formula I.



Hibbert and his co-workers¹⁹⁶ have shown that the reaction is a stepwise addition of ethylene oxide to polyethylene glycols previously produced. Flory¹⁹⁷ has studied the ratio of the weight average to the number average molecular weight in this series and finds that it approaches unity. The molecular weights vary considerably, but preparations averaging about 120,000 have been recorded. The lower polymers have molecular weights in the range up to a few thousand. The polyethylene glycols with 3, 6, 18, 42, 90, and 186 repeating units have been studied by Lovell and Hibbert.¹⁹⁸

By polymerization of ethylene oxide with alkaline catalysts, water-soluble waxes have been obtained. These are known commercially as "Carbowaxes."

Other oxides as propylene oxide may be polymerized with catalysts like stannic chloride. Cyclohexene oxide has been polymerized under pressure.¹⁹⁵ Ethylene sulfide polymerizes easily to a substance analogous to that obtained from the oxide.

Mechanism of Addition Polymerization Reactions

As has been pointed out, the reactions leading to the formation of condensation polymers are considered to be of the same nature as the corresponding simple condensation reactions of organic compounds, such as esterification, etherification, amide formation, and aldol condensation, differing only in the fact that the reactions are capable of indefinite repetition. The extensive investigations of this type of polymerization have shown^{3, 199} that the structure and size of the polymeric molecules, as well as the kinetics of their formation, are in agreement with a mechanism involving successive condensation reactions, each

¹⁹⁶ See Perry and Hibbert, *ibid.*, **62**, 2599 (1940), for leading references.

¹⁹⁷ Flory, *ibid.*, **62**, 1561 (1940).

¹⁹⁸ Lovell and Hibbert, *ibid.*, **62**, 2144 (1940).

¹⁹⁹ Flory, *ibid.*, **59**, 466 (1937) (condensation), **59**, 241 (1937) (addition).

individual step being no more unusual or complex than the ordinary reactions of organic compounds.

Addition polymerization, however, possesses certain peculiarities which clearly distinguish this type of reaction and which have led to many investigations and much speculation concerning the mechanism involved. The essential distinguishing feature is that the average molecular weight of the polymer molecules first formed is very nearly the same as the molecular weight of those formed later, in marked contrast to condensation polymerization, in which the polymeric molecules continue to increase in size during the course of the reaction. In addition to this unusual mode of formation of addition polymers, any entirely satisfactory mechanism for the formation of these substances must, of course, also be capable of accounting for such structural considerations as orientation of the monomer units, end groups, and chain branching.

The generally accepted explanation of these characteristics consists of a mechanism dividing the reaction into three steps involving (A) activation of individual monomer molecules, followed by (B) rapid reaction of the active form with successive molecules of monomer, retaining the activity, and finally (C) a loss of activity in some manner to yield a stable polymer molecule.

The intimate mechanisms of these various steps in the process, initiation (A), propagation (B), and cessation (C), have been the subjects of extensive investigation, particularly by means of kinetics, correlated with the average size and size distribution of the polymers. Styrene,^{126, 127, 128, 129, 200, 201, 202, 203, 204, 205} vinyl acetate,²⁰⁶ methyl methacrylate,^{172, 200} and dienes¹⁷² have been the monomers receiving most attention. They have been polymerized thermally or under the influence of such catalysts as peroxides,^{200, 201, 206, 207, 208} metal halides,²⁰¹ alkali metals,¹⁷⁵ light,¹⁷² or various free radicals, generated chemically^{202, 203} or photochemically.¹⁷²

The analytical procedures for following the rate of reaction have been isolation of the polymer,^{128, 201} titration of the monomer by bromine,^{201, 205} change in volume,^{206, 209} and, most recently, the change in rotation on

²⁰⁰ Norrish and Brookman, *Proc. Roy. Soc. (London)*, **A171**, 147 (1939).

²⁰¹ Schulz and Husemann, *Z. physik. Chem.*, **B39**, 246 (1938).

²⁰² Schulz and Wittig, *Naturwissenschaften*, **27**, 387, 456 (1939).

²⁰³ Schulz, *ibid.*, **27**, 659 (1939).

²⁰⁴ Williams, *J. Chem. Soc.*, 775 (1940).

²⁰⁵ Whithy, *Trans. Faraday Soc.*, **32**, 315 (1936).

²⁰⁶ Cutlbertson, Gee, and Rideal, *Proc. Roy. Soc. (London)*, **A170**, 300 (1939); Kamenskaya and Medvedev, *Acta Physicochim. (U.R.S.S.)*, **13**, 565 (1940).

²⁰⁷ Marvel, Dec, and Cooke, *J. Am. Chem. Soc.*, **62**, 3499 (1940).

²⁰⁸ Price and Kell, *ibid.*, **63**, 2798 (1941).

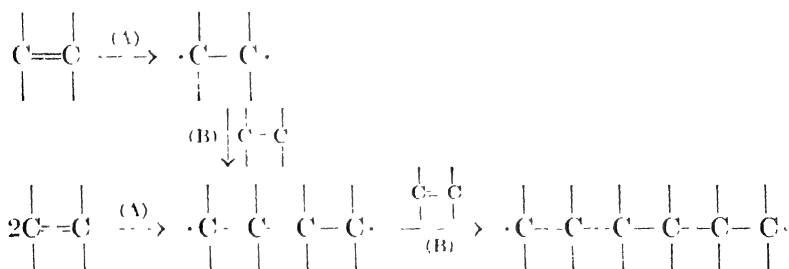
²⁰⁹ Starkweather and Taylor, *ibid.*, **52**, 4708 (1930).

polymerization of optically active monomers.^{207, 208} Owing to difficulties in analytical procedure, a majority of the investigations of the kinetics of polymerization has been carried out without a diluent^{128a, 200, 206} or over such a wide range in mole fraction of solvent^{128b, 201} that any deductions as to the mechanism are complex and difficult because of the possible effect of the change in solvent medium on the rates of the various steps involved in the reaction.

In general, there have been two essentially different viewpoints with regard to the nature of the propagation reaction. That originally proposed by Staudinger²¹⁰ and supported by many other investigators^{128, 172, 199, 200, 202, 203, 208} has indicated a specific mechanism involving addition of an active free radical to the double bond of a monomer molecule, generating a new free radical which can in turn add again to another monomer molecule. As a free radical chain reaction, polymerizations proceeding by such a mechanism should be characterized by being subject to strong inhibition by small amounts of such substances as hydroquinone or diphenylamine.²¹¹ It is a well-known fact that small amounts of hydroquinone and other substances are capable of preserving such monomers as methyl methacrylate, styrene, vinyl acetate, and dienes.

A second viewpoint regards the propagation reaction as an "energy chain,"²⁰⁵ in which an "activated" or "excited" monomer molecule adds to a normal molecule yielding an activated dimer which can add another monomer molecule, the process continuing until the activation is dissipated in some manner.

For thermal polymerization in the absence of added catalytic agents, it has been suggested that the activation process might consist in the formation of a diradical,^{201, 210} either unimolecular or bimolecular.



Burk²¹² and later Irany²¹³ have clearly pointed out that a serious draw-

²¹⁰ See Staudinger, *Trans. Faraday Soc.*, **32**, 97 (1936).

²¹¹ See, e.g., Price, *J. Am. Chem. Soc.*, **58**, 1834 (1936).

²¹² Burk, *Ind. Eng. Chem.*, **30**, 1059 (1938).

²¹³ Irany, *J. Am. Chem. Soc.*, **62**, 2690 (1940).

back to this suggestion is the absence of cyclic polymers, especially trimers, which might be expected from such diradicals.

The extensive investigations of Schulz¹²⁸ on the thermal polymerization of styrene, alone and in various solvents, have indicated that the initiation process in this case may be a unimolecular activation of styrene, leading to a free radical propagation reaction between monomer and an active chain and a cessation reaction involving mutual deactivation of two active free radical chains, either by coupling or, more probably, by disproportionation.¹⁹⁹ Breitenbach²¹⁴ has disputed the possibility of drawing any safe conclusions concerning the intimate mechanism of a reaction from kinetic data over as wide a range of solvent concentration as that employed in the investigations by Schulz, Husemann, and Dinglinger.^{128, 201} However, Schulz and Wittig^{202, 203} have clearly demonstrated the possibility of the initiation of polymerization by free radicals, using the dissociation of tetraphenylsuccinonitrile $\left[\begin{array}{cc} (\text{C}_6\text{H}_5)_2\text{C} & \text{C}(\text{C}_6\text{H}_5)_2 \\ | & | \\ \text{CN} & \text{CN} \end{array} \right]$ ²⁰² and the thermal decomposition of benzene-azotriphenylmethane $[(\text{C}_6\text{H}_5)_3\text{CN}=\text{NC}_6\text{H}_5]$ ²⁰³ as sources of free radicals. Melville¹⁷² has also used free radicals to initiate the polymerization in the gaseous phase. The sources of free radicals were the mercury-vapor-sensitized photochemical dissociation of hydrogen into atoms and the photolysis of acetaldehyde.

For the benzoyl peroxide catalysis of the polymerization of styrene, Schulz and Husemann²⁰¹ have concluded that the propagation and cessation reactions remain unaffected by the catalyst. The catalyst serves merely to increase the rate of the initiation reaction. Schulz has suggested a mechanism for the initiation reaction in the presence of peroxides involving the equilibrium formation of a complex between the catalyst and styrene, which then decomposes to give an activated styrene molecule. At constant solvent concentrations, however, his data²⁰¹ show the rate to be proportional to the square root of the catalyst concentration, in agreement with the results of Cuthbertson, Gee, and Rideal²⁰⁶ using the same catalyst with vinyl acetate. Melville²¹⁵ has pointed out that such a dependence of the rate on the catalyst concentration is strong indication of unimolecular decomposition of catalyst as the initiation process and mutual (bimolecular) deactivation of active chains as the cessation reaction. This view is supported by the kinetics of the peroxide-catalyzed polymerization of *d*-sec-butyl α -chloroacrylate in dilute dioxane solution.²⁰⁸ Price and Kell²⁰⁸ have pointed out that

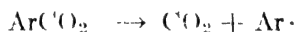
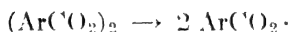
²¹⁴ Breitenbach, *Z. physik. Chem.*, **B45**, 101 (1939).

²¹⁵ Melville, *Ann. Repts. Chem. Soc. (London)*, **36**, 61 (1939).

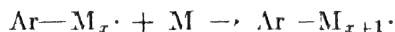
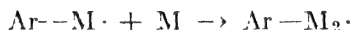
the specific nature of this unimolecular chain-initiating reaction of peroxides is most probably their decomposition into free radicals, proposed by Hey and Waters²¹⁶ to account for the thermal decomposition products of acyl peroxides in various solvents. This suggestion has offered an excellent explanation for many of the unusual catalytic effects of peroxides;^{217, 218, 219} the unimolecular nature of the process is supported by an investigation of its kinetics.²²⁰ In support of the mechanism of chain initiation by free radicals from the decomposition of the acyl peroxides is the observation that polystyrene prepared with *p*-bromobenzoyl peroxide as the catalyst contained bromine in approximately the correct amount for two halogen atoms per polymer molecule.²²¹

This free-radical mechanism of peroxide catalysis may be illustrated by the following simple equations, in which M represents the monomer molecule and the dot indicates the odd electron of the free radical:

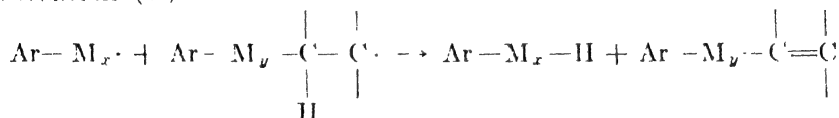
Initiation (A)



Propagation (B)



Cessation (C)



or



Individual active polymeric chains may be deactivated and transformed into stable polymer molecules in several ways. For example, the free radical may lose a hydrogen atom from the adjacent carbon atom to give a polymer molecule terminated by a double bond, or it may acquire a hydrogen atom from some other molecule in the reaction mixture to give a saturated polymer.²¹⁵ Either of these processes, how-

²¹⁶ Hey and Waters, *Chem. Rev.*, **21**, 169 (1937).

²¹⁷ Kharasch, Mausfield, and Mayo, *J. Am. Chem. Soc.*, **59**, 1155 (1937).

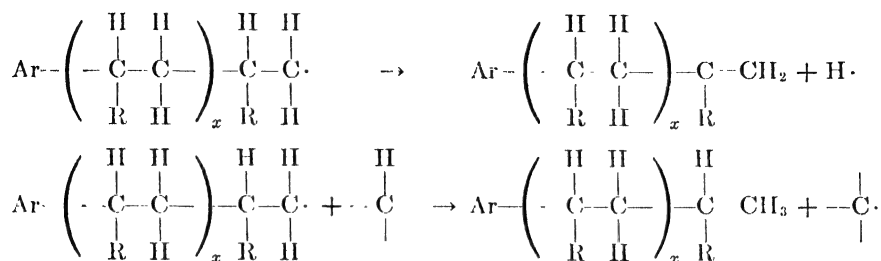
²¹⁸ Kharasch and H. C. Brown, *ibid.*, **61**, 2142 (1939), **62**, 925 (1940).

²¹⁹ Kharasch, Kane, and H. C. Brown, *ibid.*, **63**, 526 (1941).

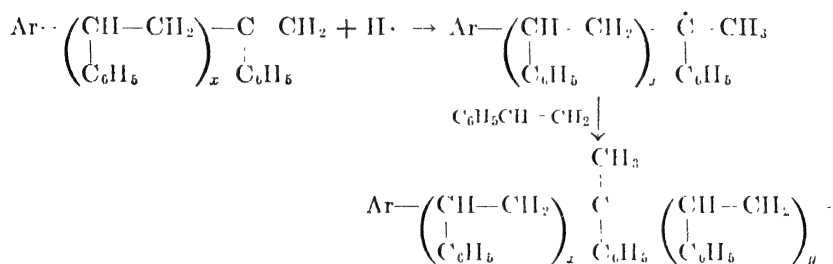
²²⁰ D. J. Brown, *ibid.*, **62**, 2657 (1940).

²²¹ Price and Kell, 101st Meeting of the American Chemical Society, St. Louis, Mo., April, 1941.

ever, is merely a *transfer* of the active free radical, not its destruction, since one of the products in each case is a radical capable of generating a new active chain.



It is significant to note that the formation of branched-chain polymers can be accounted for either by reaction of an unsaturated polymer molecule with an active chain or by means of the second transfer reaction above if the substance donating the hydrogen atom is a polymer molecule. Either or both of these reactions also account for the observed increase in molecular weight when polystyrene is treated with styrene under polymerization conditions¹²⁵ and for the occurrence of occasional methyl side groups reported on polystyrene chains.¹²¹



The nature of addition polymerization in the presence of such catalysts as boron fluoride, aluminum chloride, stannic chloride, or antimony pentachloride must involve a different sort of mechanism. Williams²⁰⁴ has measured the kinetics of the polymerization of styrene in the presence of such catalysts and found the rate to be directly dependent on the catalyst concentration.

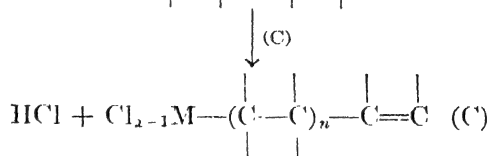
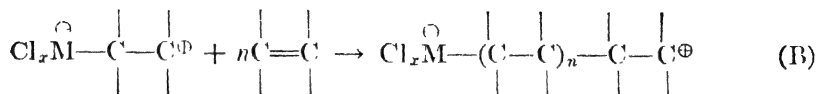
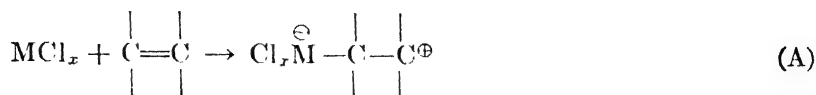
Polymerization under these conditions may involve a polar chain mechanism, initiated by reaction of the catalyst with a monomer molecule. The catalysts are, in general, also effective catalysts for the Friedel and Crafts type of reaction which depends on the electrophilic (electron-accepting) nature of the catalysts.²²²

Hunter and Yohe²²³ have suggested that the chain-initiating action

²²² See Price, *Chem. Rev.*, **29**, 37 (1941).

²²³ Hunter and Yohe, *J. Am. Chem. Soc.*, **55**, 1248 (1933).

of such catalysts depends on their electrophilic nature and consists in the acquisition by the catalyst of a pair of electrons from the double bond of the monomer.



This mechanism is thus analogous to that suggested by Whitmore²²⁴ for acid-catalyzed polymerization; in the latter case the electron-deficient (electrophilic) catalyst consists of a proton. Under conditions in which propagation is rapid compared with the loss of a proton from the active polymer, long-chain polymers would result; under conditions in which the reverse holds true, dimers and trimers would be the principal products.

If the cessation reaction were the unimolecular loss of a proton, leaving a double bond at the end of the chain, the observations of Williams,²⁰¹ i.e., that the rate is directly dependent on catalyst concentration, while the degree of polymerization is independent of catalyst concentration, would be accounted for. Furthermore, the polymer would be an organometallic compound, which may account for the difficulty encountered in freeing such polymers from the catalyst.

In addition to the kinetics of the reaction, an entirely satisfactory mechanism for polymerization must account for the structure of the polymer obtained. In general, monomers with polarized double bonds, i.e., those containing negative groups attached at one end of the vinyl grouping, such as styrene, acrylic esters, and vinyl esters, might be expected to polymerize in a head-to-tail fashion, regardless of which reaction mechanism is considered. This has been found to be true for most of the addition polymers which have been investigated. The α -haloacrylates,¹⁵³ which polymerize head-to-head, tail-to-tail, appear to be an exception to the general behavior of this type of compound, and there is at present no satisfactory explanation for this.

²²⁴ Whitmore, *Ind. Eng. Chem.*, **26**, 94 (1934).

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CHAPTER 9

CATALYTIC HYDROGENATION AND HYDROGENOLYSIS

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AND

RALPH L. SHRINER, *Indiana University*

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INTRODUCTION

The reduction of organic compounds may be accomplished by either of two general methods: (a) treatment with chemical reducing agents or (b) reaction with molecular hydrogen in the presence of a catalyst. The second process is termed *hydrogenation* when hydrogen is added to a double or triple linkage. Cleavage of a molecule by combination with hydrogen in the presence of a catalyst is termed *hydrogenolysis*. Both these processes have been proved to be valuable tools in synthetic organic chemistry. It is the purpose of this chapter to provide the fundamental background for an understanding of these reactions and for their employment in the laboratory.

The number and nature of the publications in this field are such that no critical or comprehensive survey can be made at the present time. Books by Sabatier-Reid (1922) and especially by Ellis (1930) give a general idea of the historical development and wide application of the catalytic combination of hydrogen with organic compounds. Recent developments are summarized in the *Reports of the Committee on Catalysis* published by the National Research Council. The present discussion will therefore be limited to the consideration of the reduction of common functional groups, in the presence of the catalysts, nickel, copper chromite, platinum, and palladium, with such comments on the experimental conditions, temperature, pressure, and solvents as may be necessary.

GENERAL METHODS AND APPARATUS

Four general methods for carrying out the reaction are used.

1. A mixture of hydrogen and the vapors of the organic compound are passed through a tube containing the catalyst maintained at a suitable reaction temperature, 20° to 400°. The proper rate of flow must be determined in order that complete reduction will be effected. This method, introduced by Sabatier in 1897, is not applicable to non-volatile substances, is difficult to control, and hence is of limited application.

2. Hydrogen is bubbled through the compound dissolved in a solvent in which the catalyst is suspended. Atmospheric pressure and temperatures ranging from 20° to the boiling point of the compound or the solution may be used. This procedure is wasteful of hydrogen and difficult to control. It is used to a limited extent in a few reductions such as the Rosenmund (p. 808).

3. The compound or a solution of the compound is agitated vigorously with the catalyst and hydrogen at a pressure of 1 to 4 atmospheres and temperatures of 20° to 60°. Usually the process is carried out in a heavy-walled glass bottle mounted in a shaking device and attached to a small hydrogen cylinder fitted with a pressure gauge. A convenient apparatus is shown in Fig. 1.

Once the apparatus has been calibrated, the course of the reduction is followed by noting the fall in pressure. This method is useful for the reduction of functional groups which are easily reduced at low pressures and temperatures with catalysts which are active at 20° to 60° such as platinum, palladium, and Raney nickel. Because of the limited pressure and temperature ranges this method cannot be used for the more difficult hydrogenations or hydrogenolyses.

4. The fourth process consists in agitating the compound or a solution of the compound and the catalyst with hydrogen at high pressures, 50 to 300 atmospheres, and at temperatures ranging from 20° to 400°. A special steel reaction bomb is used fitted with a pressure gauge as shown in Fig. 2. The vessel is mounted in an electrical heating jacket the temperature of which is controlled by means of a thermocouple and electrical control system. One convenient type of apparatus is shown in Fig. 3. The course of the reduction is followed by noting the pressure drop at the operating temperature. Usually it is convenient to calibrate each bomb at several temperatures with a known compound.

This fourth procedure was introduced by Ipatieff in 1904 but was not widely used until the improvements in the alloys for the bombs and design of reaction equipment made high-pressure reductions relatively inexpensive, convenient, and safe. A detailed description of the apparatus and a summary of reductions by this fourth process have been given by Adkins.

From the practical point of view, methods 3 and 4 above have proved to be of greatest utility in the laboratory. Most of the reductions described in this chapter were carried out by one of these methods.

In order to effect complete reductions smoothly in the minimum amount of time, it is necessary that the compound being reduced be pure and that a pure solvent be employed. All catalytic processes are

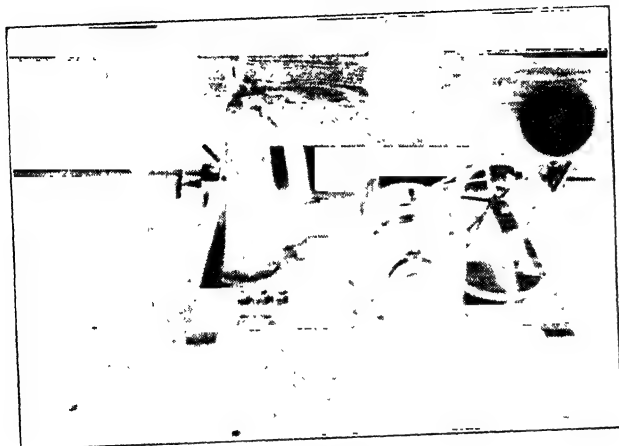


FIG. 1.

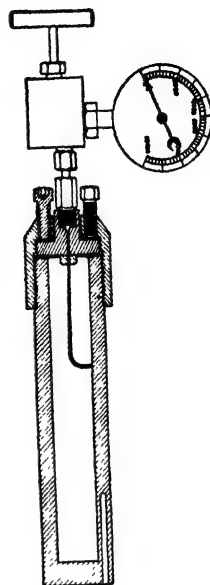


FIG. 2.

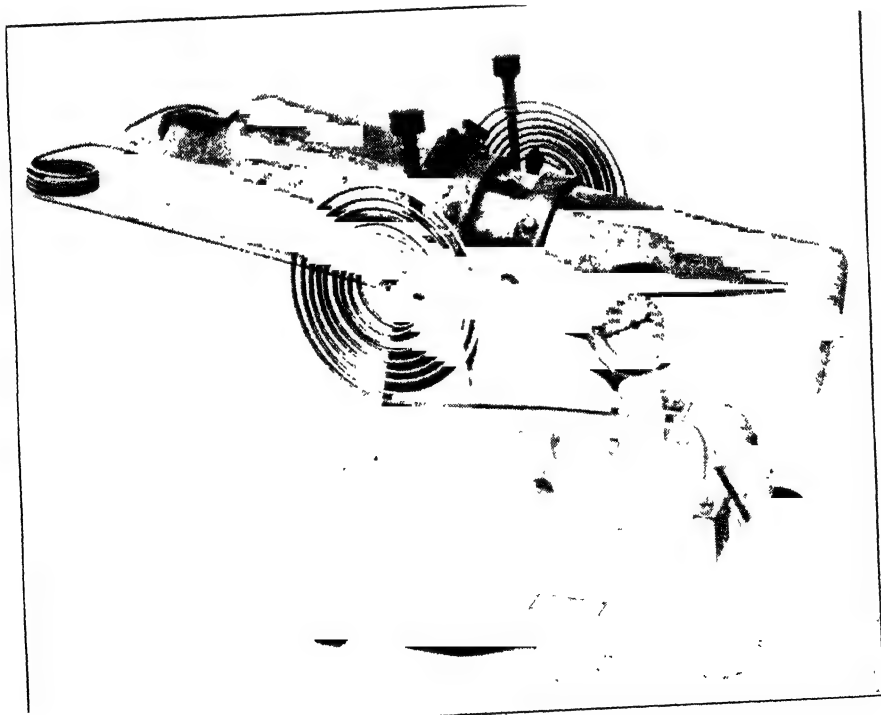


FIG. 3.

adversely affected by "poisons"; care must therefore be taken to keep the apparatus clean, to use pure compounds, and to prepare the catalyst by following exactly the procedures which have been found to produce active catalysts.

PREPARATION OF CATALYSTS

Colloidal Forms

Platinum. Paal^{1, 2} prepared a platinum sol by adding hydrazine hydrate to chloroplatinic acid dissolved in a 2 per cent solution of sodium protalbate or lysalbate neutralized with alkali. After reduction was complete the salts were removed by dialysis and the solution evaporated. Black platinum solutions containing from 6 to 78 per cent platinum were obtained. These colloids are precipitated by acids. Reduction of a 1 per cent solution of chloroplatinic acid by hydrogen in the presence of gum arabic³ yields a colloidal sol stable in the presence of acids. Colloidal forms of platinum have also been prepared using lanolin^{4, 5, 6} as a protective agent. Colloidal hydrosols of platinum hydroxide have also been prepared.⁶

Palladium. Colloidal sols containing up to 67 per cent palladium protected by sodium protalbate were prepared by Paal² by the same procedure described above for platinum. Gum arabic,³ soluble starch,^{7, 8} and gluten⁹ have been used as protective agents to obtain colloidal suspensions of finely divided palladium. Palladous hydroxide stabilized by gum arabic⁶ or lanolin⁵ has also been used. An organosol of palladium oleate may be obtained by the action of sodium oleate on ammonium palladium chloride.¹⁰

These colloidal sols of platinum and palladium were used as catalysts in many of the early reductions but are not widely used at the present time because difficulties are experienced in obtaining a uniformly active catalyst and in isolating the products from reductions.

¹ Paal, *Ber.*, **35**, 2195 (1902).

² Paal and Amberger, *Ber.*, **37**, 124 (1904).

³ Skita and Meyer, *Ber.*, **45**, 3589 (1912).

⁴ Amberger, *Kolloid-Z.*, **13**, 310 (1913).

⁵ Paal and Amberger, U. S. pat., 1,077,891 (1913).

⁶ Skita and Meyer, *Ber.*, **45**, 3579 (1912).

⁷ Bourguet, *Bull. soc. chim.*, [4] **41**, 1443 (1927).

⁸ Bourguet, *ibid.*, [4] **43**, 231 (1928).

⁹ Kelber and Schwarz, *Ber.*, **45**, 1946 (1912).

¹⁰ Sulzberger, U. S. pat., 1,171,902 (1916).

Amorphous Forms

Platinum Black. 1. *By the Reduction of Soluble Salts.* Platinum black is usually prepared by the method of Loew,¹¹ whose procedure has been modified by Willstätter and Hatt,¹² by Willstätter and Waldschmidt-Leitz,¹³ and again by Feulgen.¹⁴ According to the procedure of Feulgen, a 50 per cent solution of chloroplatinic acid is reduced by means of a 40 per cent formaldehyde solution made strongly alkaline with sodium hydroxide. After thorough washing the reduced metal is dried in a vacuum desiccator over sulfuric acid.

Some hydrogenations may be carried out successfully by reducing a platinum salt with hydrogen in the presence of the material to be hydrogenated. According to the procedure of Paal¹⁵ a variety of platinum compounds such as chloroplatinic acid, potassium chloroplatinate, platinous chloride, etc., may be added in powdered form, in aqueous solution, or suspended in fat or mineral oil, to an unsaturated fat or fatty acid. Hardening of the fat takes place when hydrogen is passed into the mixture under a pressure of 2–3 atmospheres at 80° C. The water is evaporated out first if an aqueous solution of the catalyst has been used. Paal recommends addition of sodium carbonate to neutralize the acid liberated when the platinum salts are reduced, but Skita¹⁶ has described a similar procedure in which no alkali is used and hydrochloric acid is sometimes added. Skita adds the platinum salts in aqueous solution and does not remove the water prior to the reduction.

2. *By Reduction of Oxides.* The oxides of platinum, which are easily reduced by hydrogen at room temperature to the amorphous form of the metal, are good hydrogenation catalysts.¹⁷ The most active catalyst is obtained from platinum dioxide which is prepared by fusion of chloroplatinic acid with an excess of sodium nitrate at 500 to 550° C. according to the procedures developed by Adams, Voorhees, and Shriner.^{18, 17, 19} The melt is allowed to cool and is dissolved in water; the hydrated platinum dioxide is removed by filtration and thoroughly washed with

¹¹ Loew, *Ber.*, **23**, 289 (1890).

¹² Willstätter and Hatt, *Ber.*, **45**, 1471 (1912).

¹³ Willstätter and Waldschmidt-Leitz, *Ber.*, **54**, 113 (1921).

¹⁴ Feulgen, *Ber.*, **54**, 360 (1921).

¹⁵ Paal, U. S. pat., 1,023,753.

¹⁶ Skita, U. S. pat., 1,063,746 (1913); French pat., 447,420 (1912); Brit. pat., 28,754 (1912); Brit. pat., 18,996 (1912); *J. Soc. Chem. Ind.*, **32**, 253 (1913); Brit. pat., 16,283 (1913).

¹⁷ Adams and Shriner, *ibid.*, **45**, 2171 (1923).

¹⁸ Voorhees and Adams, *J. Am. Chem. Soc.*, **44**, 1397 (1922).

¹⁹ "Organic Syntheses," Collective Vol. 1, John Wiley & Sons, New York (1932), p. 452. See also Cook and Linstead, *J. Chem. Soc.*, 952 (1934); Bruce, *Org. Syn.*, **17**, 98 (1937).

1 per cent sodium nitrate solution. The oxide is readily reduced to platinum black when a suspension of it is shaken with hydrogen. The oxide may be reduced before addition of the compound being hydrogenated, or it may be added along with the compound and then shaken with hydrogen.

3. Supported Platinum Catalysts. Platinum black is often precipitated on an inert carrier when it is used as a hydrogenation catalyst. Among the materials most frequently used as carriers are barium sulfate, activated charcoal, calcium carbonate, kieselguhr, and silica gel. The inert material is suspended in a weak solution of chloroplatinic acid and warmed for several hours at 40–50°. Sodium carbonate solution is then added to neutralize the acidity. The platinum is precipitated on the carrier in the form of the hydroxide. The catalyst can be filtered, washed with water, and dried in a vacuum desiccator. Enough chloroplatinic acid is usually used to give a product containing 2–5 per cent of platinum.^{20, 21} A platinum catalyst employing silica gel as a carrier has been prepared by Reyerson and his co-workers^{22, 23, 24} by evacuating silica gel to remove the air, then saturating with hydrogen at a temperature of 15–30°, and treating with a platinous solution obtained by reducing chloroplatinic acid with sulfur dioxide. The platinum is reduced to the free metal by the hydrogen in the gel.

Asbestos has also been employed as a carrier for platinum black. The asbestos is usually soaked in a solution of chloroplatinic acid, and the metallic platinum is deposited by reduction with formaldehyde and alkali,²⁴ or by reduction with hydrogen at 150° C. after the asbestos has been dried.²⁵

Zeolites have been used as carriers for platinum. The artificial zeolite, sodium permutite, can be heated until most of the water is driven out and then soaked in a solution of chloroplatinic acid. Drying and heating, followed by removal of soluble salts by washing, gives a platinum zeolite.²⁶

Palladium Black. *1. By Reduction of Soluble Salts.* Palladium black is often prepared by the reduction of solutions of palladium salts with sodium formate or with formaldehyde.²⁷ The sodium formate reduction

²⁰ Houben-Weyl, "Die Methoden der organischen Chemie," Vol. 2, p. 499.

²¹ Kaffer, *Ber.*, **57**, 1261 (1924).

²² Latshaw and Reyerson, *J. Am. Chem. Soc.*, **47**, 610 (1925).

²³ Morris and Reyerson, *J. Phys. Chem.*, **31**, 1220 (1927), *J. Inst. Petroleum Tech.*, 221A (1927); *J. Phys. Chem.*, **31**, 1332 (1927).

²⁴ Zelinsky and Turova-Pollak, *Ber.*, **58**, 1298 (1925).

²⁵ Barratt and Titley, *J. Chem. Soc.*, **115**, 902 (1919).

²⁶ Mittasch, Schneider, and Morawitz, U. S. pat., 1,215,396 (1917); Brit. pat., 1,358 (1915).

²⁷ Houben-Weyl, "Die Methoden der organischen Chemie," Vol. 2, p. 498.

is carried out by slow addition of formic acid to a solution of palladium chloride made somewhat basic with sodium hydroxide. Reduction by formaldehyde is carried out by addition of 33 per cent formaldehyde solution and a 50 per cent potassium hydroxide solution to a dilute solution of palladous chloride containing hydrochloric acid. In either procedure the palladium black is filtered from the solution, washed with water on the filter, and dried over sulfuric acid *in vacuo*.

With palladium, as with platinum, some hydrogenations may be carried out by mixing palladous salts with the material to be hydrogenated. Procedures have been worked out by Paal¹⁵ and Skita¹⁶ which are the same as those described above in which platinum salts were used.

2. By Reduction of Oxides. An active palladium black catalyst is obtained when palladous oxide, prepared by the method of Shriner and Adams,^{19, 28} is reduced by hydrogen in the presence of the substance to be hydrogenated. Palladous chloride is fused with sodium nitrate, and the temperature is raised to 575–600° to produce palladous oxide. The melt is cooled and treated with distilled water. The oxide is removed by filtration and washed with a 1 per cent solution of sodium nitrate.

3. Supported Palladium Catalysts. Barium sulfate often serves as a carrier for palladium when it is used as a hydrogenation catalyst. The usual method for the preparation of this catalyst is that of Schmidt.^{28, 29} Barium sulfate which has been precipitated from a hot solution is suspended in water and treated with a dilute solution of palladous chloride. The palladium is reduced to the free metal by addition of a solution of formaldehyde (40–50 per cent) made alkaline to litmus with sodium hydroxide; the mixture is boiled until the solution becomes colorless. The catalyst, a gray residue, is then filtered off, washed thoroughly with hot water, and dried in a desiccator over potassium hydroxide.

Various types of activated charcoal have served as carriers for palladium. Several methods of preparation have been developed,^{30, 31, 32} but those used by Hartung³³ and by Ott and Schröter³⁴ are perhaps the simplest and best. Activated charcoal is shaken with a solution of palladous chloride in an atmosphere of hydrogen until saturated. The charcoal containing the palladium is filtered, washed, dried, and kept in a vacuum desiccator.

²⁸ Shriner and Adams, *J. Am. Chem. Soc.*, **46**, 1683 (1924).

²⁹ Schmidt, *Ber.*, **52**, 409 (1919), Ger. pat., 252,136.

³⁰ Sabalitschka and Moses, *Ber.*, **60**, 800 (1927).

³¹ Mayer and Stumm, *Ber.*, **56**, 1424 (1923).

³² Mannich and Thiele, *Ber. deut. pharm. Ges.*, **26**, 36 (1916).

³³ Hartung, *J. Am. Chem. Soc.*, **50**, 3370 (1928); *J. Soc. Chem. Ind.*, 548 (1916).

³⁴ Ott and Schroter, *Ber.*, **60**, 633 (1927).

Calcium carbonate has also been used as a support for a palladium catalyst. According to the method of Busch and Stöve,³⁵ calcium carbonate prepared by the treatment of a hot solution of calcium chloride with sodium carbonate is suspended in water and a solution of palladous chloride is added. The mixture is gently warmed until the palladium is deposited on the carbonate as palladous hydroxide, and the catalyst is washed a few times with distilled water by decantation. It is then filtered, washed on the filter until free of chlorides, using as little water as possible, and dried. Reduction of the palladous hydroxide takes place during hydrogenation.

Palladium catalysts supported on silica gel have been described.²⁰ Latshaw and Reyerson²² have prepared such a catalyst in the same manner as they prepared their platinum-silica gel catalyst described above. Silica gel which has been exhausted in a vacuum and then saturated with hydrogen is treated with a solution of ammonium chloropalladite. The palladium is reduced by the hydrogen and deposited on the gel. The catalyst is then washed and dried.

Kieselguhr is another support which has been used for palladium. Sabalitschka and Moses³⁰ prepared such a catalyst by shaking kieselguhr with a very dilute solution of palladous chloride until all the salt was adsorbed, then reducing by shaking the suspension with hydrogen. The catalyst was then filtered from the solution, washed thoroughly with water, and dried.

Palladium zeolites have been prepared and reduced to give a supported palladium catalyst.²⁶ Sodium permutite is digested with a dilute solution of palladous chloride containing a little hydrochloric acid until the palladous ion is removed from solution. (The solution becomes colorless.) The material is washed thoroughly and then reduced with hydrogen at 150–200° or with formaldehyde at a lower temperature.

Schwareman³⁶ has suggested metallic sesquioxides such as aluminum oxide as carriers. This catalyst was prepared by precipitation of a 10 per cent solution of aluminum sulfite by its equivalent of 20 per cent sodium hydroxide at 77° C. After the precipitate is washed it is boiled with a 0.3 per cent solution of palladous chloride. The catalyst is filtered, washed, and dried at 77° C. A platinum catalyst may be prepared in similar fashion, but is less active.

Nickel. Until recent years the type of nickel catalyst most commonly used in the laboratory was prepared by reducing with hydrogen a nickel compound which had been deposited on a suitable inert, porous support. The support was impregnated with a nickel salt, and then nickel hydrox-

³⁵ Busch and Stöve, *Ber.*, **49**, 1063 (1916).

³⁶ Schwareman, U. S. pat., 1,111,502 (1914).

ide or carbonate was precipitated by the addition of sodium or ammonium hydroxide or carbonate. The support was then washed free of soluble salts and dried, and the resulting nickel oxide was reduced with hydrogen at 300° to 450°. In order to facilitate the washing process the use of nickel nitrate and ammonium carbonate has been recommended, but if the cost of the salts is an important factor the sulfate or chloride and sodium hydroxide is satisfactory. The activity of the catalyst is determined by many details such as the type of support, the exact procedure followed, the purity of the reagents, the temperature and rate of reduction of the nickel oxide, and the presence of other oxides. A satisfactory procedure for the preparation of nickel on kieselguhr has been described.³⁷

Raney Nickel. The most common nickel catalyst today is that prepared according to a process invented by Murray Raney.³⁸ It is commercially available as an alloy containing approximately equal weights of nickel and aluminum and corresponding to the formula NiAl_2 . The aluminum is dissolved out of the alloy with sodium hydroxide, and the residual nickel, after thorough washing, is stored under water, alcohol, ether, dioxane, methyleyclohexane, or other liquid. A suitable procedure for the preparation of the catalyst from the alloy is described by Mozingo.³⁹ The Raney nickel catalyst is active for some compounds at lower temperatures than the supported nickel catalyst, and it is much more accessible and convenient. It is not so readily suspended in a reaction mixture, and the amount of nickel required for a given hydrogenation is many times greater than for a nickel on kieselguhr catalyst.

Cobalt has often been suggested as equal to or superior to nickel as a catalyst for certain types of hydrogenation, but there appears to be no unequivocal evidence on this point.

The addition of other metals such as copper, zinc, chromium, molybdenum, iron, cerium, occasionally seems to improve the catalytic action of nickel. G. B. L. Smith and associates⁴⁰ in recent years have published a series of papers in which are described the beneficial effects of adding platinum to Raney nickel.

Copper Chromite. A large number of oxides, such as zinc oxide, nickel oxide, copper oxide, chromium oxide, and molybdenum oxide, for instance, are catalysts for hydrogenation, but in general they suffer from two disadvantages. They either require a high temperature (300° to 500°), or else they are readily deactivated by reduction. Copper oxide

³⁷ Covert, Connor and Adkins, *J. Am. Chem. Soc.*, **54**, 1651 (1932), also p. 19. "Reactions of Hydrogen."

³⁸ Murray Raney, U. S. pat., 1,628,190 (May, 1927).

³⁹ Mozingo, *Org. Syntheses*, **21** (1941), John Wiley & Sons, New York.

⁴⁰ Reasenberg, Lieber, and Smith, G. B. L., *J. Am. Chem. Soc.*, **61**, 384 (1939).

in particular suffers under the second handicap, but if it is combined with chromium oxide it is stabilized against reduction without losing its catalytic activity. Presumably, the catalyst is present as copper chromite CuCr_2O_4 (Gröger)⁴¹. The presence of small amounts of barium or calcium chromite in the catalyst mass tends to stabilize the divalent copper against reduction. The catalyst may be made in many different ways, but the most satisfactory method is by the thermal decomposition of copper ammonium chromate,⁴² prepared by mixing water solutions of a copper salt, a chromate, and ammonium hydroxide. It is not necessary to wash the precipitate, but only to dry it and heat it to a suitable temperature (150–250°), when it decomposes rather violently. The catalyst is then washed with dilute acetic acid and water and dried. The finely divided black catalyst may be kept indefinitely.

Copper chromite is active in the temperature range of 100° to 300° but usually requires hydrogen pressures of 100 to 300 atm. At temperatures above 300°, or in the presence of water, acids, or ammonia, it is likely to be reduced to a red cuprous compound which has little catalytic activity for hydrogenation.

Other Oxides. Zinc oxide is active as a catalyst for hydrogenation from 300° to 400°. Zinc chromite has been particularly useful for the hydrogenation of carbon monoxide to methanol. Zinc chromite is also active for the hydrogenation of esters to alcohols at 300° to 350°. It is noteworthy that by its use an unsaturated ester such as ethyl oleate can be hydrogenated to the corresponding unsaturated oleyl alcohol.⁴³ However, the product always contains considerable quantities of the saturated octadecyl alcohol. Molybdenum sulfide has been recommended for the hydrogenation of sulfur-containing compounds at 350° to 400°.

Patent claims for these and many other substances have been made. Unquestionably, many compounds not mentioned above have merit as catalysts for hydrogenation, dehydrogenation and disproportionation, especially for temperatures above 300°; but platinum, palladium, nickel, and copper chromite are certainly the most useful catalysts in the organic laboratory at the present time. A table showing over sixty hydrogenation catalysts with comments on their preparations, activities, and uses is given by Williams and Beeck.⁴⁴

⁴¹ Gröger, *Z. anorg. Chem.*, **58**, 412 (1908); **76**, 30 (1912).

⁴² Connor, Folkers, and Adkins, *J. Am. Chem. Soc.*, **54**, 1138 (1932), also p. 13, "Reactions of Hydrogen." Lazier and Arnold, *Org. Syn.*, **19**, 31 (1939).

⁴³ Sauer and Adkins, *J. Am. Chem. Soc.*, **59**, 1 (1937).

⁴⁴ Williams and Beeck, "Twelfth Report of the Committee on Catalysis," p. 114. John Wiley & Sons (1940).

THE ROLE OF THE CATALYST IN HYDROGENATION

The following discussion outlines a working concept of the role played by the catalyst in hydrogenation.⁴⁵ The hypothesis suggested rationalizes a multitude of observations, many of which are otherwise anomalous. No attempt will be made to enter into the fine details of the mechanism of catalysis. It will be assumed that we are concerned with the ordinary chemical reactions of hydrogen, catalyst, and hydrogen acceptor with one another.

A catalyst may be defined as a substance that accelerates or causes a reaction to take place. Catalysis is concerned with the influence of one molecule upon the behavior of another molecule. This definition assumes that two molecules, such as those of hydrogen and ethylene, do not react with each other except under the influence of a third substance, such as nickel. The catalysts for hydrogenation apparently function by combining with the hydrogen and with the compound to be hydrogenated (hydrogen acceptor). The result of this combination with the catalyst is that the hydrogen and hydrogen acceptor react with each other. Simply expressed, molecules of hydrogen and molecules of ethylene are inert toward each other, but hydrogen attached to nickel may react with ethylene attached to nickel to give ethane. The ethane then leaves the nickel, permitting the metal to react with more ethylene and hydrogen and so repeat the process of hydrogenation.

What are the characteristics of a "good" or effective catalyst upon the basis of this simple concept of the role of the catalyst? First, a good catalyst must be stable under reaction conditions, and many of the things that are done in preparing and using a catalyst are connected with stabilizing it against change. Probably many so-called promoters merely tend toward stabilizing the catalyst rather than enhancing its activity. Certain catalysts, especially those used in catalytic oxidation, such as copper, silver, vanadium oxide, and molybdenum-iron oxide, are constantly renewing their surfaces by alternate oxidation and reduction.

A change in experimental conditions may render a catalyst useless because it can no longer maintain the active form. For example, copper chromite, an excellent catalyst for hydrogenation in the liquid phase, in many cases is not so satisfactory in the gas phase. This is because the divalent copper in the active catalyst is more readily reduced by hydrogen if the copper chromite is not wet. An excess of water facilitates the dehydration of alcohols over alumina, whereas an excess of ammonia is

⁴⁵ Adkins, *Ind. and Eng. Chem.*, **32**, 1189 (1940).

advantageous in dehydrogenating amines. These various reagents probably improve the processes because they maintain the catalyst in the proper state of oxidation or because they prevent the accumulation of by-products on the active surface.

A good catalyst for hydrogenation must combine several distinct characteristics or abilities in addition to maintaining its active state under reaction conditions.

1. It must adsorb and activate hydrogen.
2. It must adsorb and activate the hydrogen acceptor.
3. It must hold them in the proper ratio and space relationship.
4. It must desorb the reduced compound.

The present discussion is primarily concerned with several types of observations, which may be rationalized in terms of the sequence of reactions on the catalyst outlined above. First, consider an example of the results of a variation in the proportion of the hydrogen and hydrogen acceptor on the surface of the catalyst, as described by Craxford,⁴⁶ for the Fischer-Tropsch synthesis of hydrocarbons. In this process carbon monoxide and hydrogen at atmospheric pressure are passed over a cobalt, iron, or nickel catalyst held at about 200°. During the first few hours after the catalyst is put into service there is a large amount of hydrogen on the catalyst, and methane is the chief product. After a time the amount of hydrogen on the catalyst is much less than in the early stages, and hydrocarbons containing many carbon atoms in each molecule are produced. That is, in the early stages with an abundance of hydrogen on the catalyst, there is no opportunity for carbon atoms to combine with one another to form long chains, for each carbon (as cobalt carbide) is adjacent to adsorbed hydrogen so that methane is the main product. After the first few hours of use there is less hydrogen on the catalyst and therefore more chance for synthesis by interaction of adjacent carbon atoms. In the above instance the change in the proportion of products is due to the change in the surface of the catalyst so that after a time hydrogen is held in lesser amounts than by the newly prepared catalyst.

The proportion of the products from the hydrogenation of a given compound may also be rather profoundly modified by a variation in the pressure of hydrogen. For example, at 120 atmospheres, α -oximinoacetoacetic ester gives mainly a pyrazine, formula I, when hydrogenated over nickel at 80°; at 320 atmospheres the hydrogenation gives α -amino- β -hydroxybutyric ester, formula II:⁴⁷

⁴⁶ Craxford, *Trans. Faraday Soc.*, **35**, 946 (1939).

⁴⁷ Adkins and Reeve, *J. Am. Chem. Soc.*, **60**, 1328 (1938).

nickel is somewhat intermediate in its pressure requirements. These observations are understandable if it is assumed that platinum and palladium take up enough hydrogen at atmospheric pressure in proportion to the amount of hydrogen acceptor adsorbed, whereas copper chromite does not have sufficient hydrogen on its surface except at relatively high pressures.

With a given catalyst the effectiveness of increased pressure of hydrogen varies with the particular hydrogen acceptor involved. For example, higher pressures of hydrogen are much more important with esters such as ethyl trimethylacetate or diethyl camphorate than with straight-chain esters which have no branching on the carbon atom alpha to the carboxy group. This observation is understandable in terms of the picture of the reaction process sketched above. In order for reaction to take place, hydrogen must be adsorbed on "active centers" of the catalyst sufficiently close to the carboxy group for reaction. The branched-chain esters will tend to cover a larger area of the catalyst than the straight-chain esters. Therefore a higher pressure of hydrogen is required to overcome the shielding effect of the branched chains on active centers of the catalyst adjacent to the carboxy group.

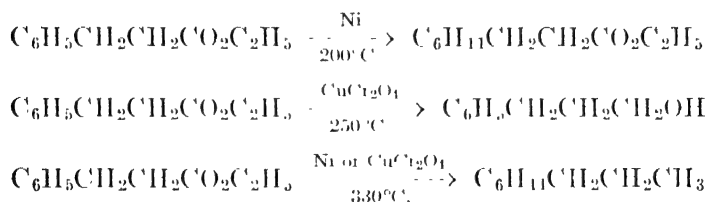
The commonly accepted picture of the surface of the catalyst is one in which active centers for adsorption are distributed over the surface. The active centers presumably consist of atoms whose valence forces are not entirely satisfied by other atoms in the surface of the catalyst. These active centers vary in activity. For example, a given center may be sufficiently active to combine with ethylene but not with hydrogen, whereas another center may be so strong that it will hold hydrogen as well as ethylene. The activity of these centers may change with the use of the catalyst, as has been illustrated in the case of the catalyst for the Fischer-Tropsch process. The number of centers of a given degree of activity available per unit area of the catalyst is often small. Almquist and Black⁴⁹ concluded that in the hydrogenation of nitrogen to ammonia only one in two thousand atoms of iron in the catalyst mass was active. The number and activity of the active centers in a catalyst are determined in part by the particular procedure followed in the preparation of the catalyst.

There are no experimental methods which show conclusively that the spacing of the active centers on the catalyst determines the rate or direction of the reactions brought about by the catalyst. By inference, many facts suggest that the space relations on the catalyst surface are of primary importance. The variation in relative reactivity among organic compounds with variation in the size and shape of molecules shows con-

⁴⁹ Almquist and Black, *ibid.*, **48**, 2814 (1936).

clusively that steric factors may determine the speed of reaction and the proportion of products, as illustrated by differences between the behavior of geometrical isomers in catalytic hydrogenation. If variation in the configuration of the hydrogen acceptor plays a role in the catalytic reaction, it is but reasonable to conclude that a similar type of variation in the catalyst will also be a factor in the process. The soundness of this conclusion is borne out by the fact that *d*-quartz will preferentially dehydrate one of the enantiomorphs of 2-butanol.⁵⁰

One of the most striking facts about catalytic hydrogenation is the selectivity that is shown by the catalyst and the hydrogen acceptor. Nickel is more active toward carbon-to-carbon double bonds than it is toward the carbonyl grouping, whereas copper chromite is more active toward carbon-to-oxygen than toward carbon-to-carbon double bonds. However, both catalysts will cause the hydrogenation of both types of unsaturation so that the difference between the catalysts is quantitative rather than qualitative. For example, the ring in ethyl β -phenylpropionate is hydrogenated over nickel at 200° to give ethyl β -cyclohexylpropionate. Over copper chromite at 250° the carboxy group of ethyl β -phenylpropionate is hydrogenated and γ -phenylpropyl alcohol is produced. At temperatures above 330° both types of hydrogenation occur over either catalyst, but a third type of reaction ensues so that the product of the hydrogenation is largely the hydrocarbon propylcyclohexane:



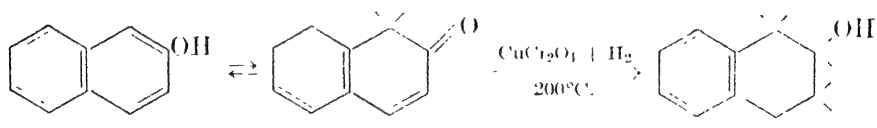
This relative inactivity of oxide catalysts toward alkene linkages is so marked in zinc chromite that the esters of the unsaturated acids such as oleic acid may be hydrogenated to unsaturated alcohols at a temperature of 250°. This is above that at which nickel would induce rapid hydrogenation of the alkene linkage in the oleate.

This selectivity in action, upon the basis of the hypothesis outlined above, is probably dependent upon preferential combination with the catalyst. That is, nickel tends to attach the hydrogen acceptor to itself at alkene or benzenoid linkages, whereas copper chromite shows a greater affinity for carbonyl groups as compared to carbon-to-carbon double bonds. The higher the temperature, the less selective the catalyst and

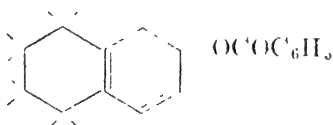
⁵⁰ Schwab and Rudolph, *Naturwissenschaften*, **20**, 363 (1932).

the greater the probability that the hydrogenation will go to the ultimate stage of the saturated hydrocarbons.

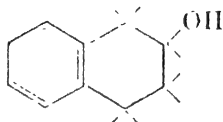
In considering the role of the catalyst, one should not ignore the variations which are possible in the structure of a given reactant. A catalyst such as copper chromite which is rather inactive toward the benzenoid nucleus may bring about such a hydrogenation through a tautomeric form of the hydrogen acceptor. The ethyl ether of β -naphthol does not react with hydrogen over copper chromite at 200° . However, β -naphthol is readily converted to 1,2,3,4-tetrahydro-2-naphthol at 200° over copper chromite.⁵¹ Presumably this is because β -naphthol may tautomerize to an unsaturated ketone, a type of compound which is rapidly hydrogenated over this catalyst:



There is little difference in rate of hydrogenation over nickel between the naphthol and its ethers, since nickel is as effective toward the benzenoid nucleus of the naphthol or its ether as it is toward the unsaturated ketone of the tautomer. However, over nickel the benzoate of β -naphthol behaves very differently from β -naphthol. Wilds⁵² has shown that the hydrogenation of the benzoate over nickel gives mainly



while Musser⁵¹ obtained



from β -naphthol.

In general, catalysts serve only to decrease the time required for the system to reach equilibrium, but instances are known where the concentrations of reactants attained from a catalyst are not the same as those that would be anticipated if the role of the catalyst were ignored. For example, Reid⁵³ reported that he had obtained ethyl acetate in yields above 80 per cent by passing equimolecular amounts of acetic acid and

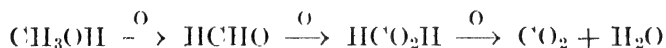
⁵¹ Musser and Adkins, *J. Am. Chem. Soc.*, **60**, 664 (1938).

⁵² Alfred Wilds, unpublished work at University of Wisconsin.

⁵³ Tidwell and Reid, *J. Am. Chem. Soc.*, **53**, 4353 (1931).

alcohol over silica gel. These results were criticized because it was pointed out that the maximum concentration of ethyl acetate could be no more than 67 per cent in a system starting with a mole each of alcohol and acid. Reid's results have been fully confirmed, and the reason for the apparent exception to the prediction based on results in a homogeneous system is easily seen if the process of esterification over a solid catalyst is similar to that outlined above for hydrogenation. Alcohol and acetic acid passing over silica gel would each be adsorbed, reaction would occur between molecules of alcohol and acetic acid adsorbed on adjacent active points on the catalyst, and then the ethyl acetate and water so produced would be desorbed. If alcohol and acetic acid were irreversibly adsorbed and water and ethyl acetate were rapidly desorbed, then the yield of ester would be 100 per cent. No such catalyst is known or likely to be found, but it will be obvious that the yield of ester is determined not by the thermodynamics of the alcohol-acid-water-ester system, but simply by the relative adsorption by the catalyst of the reactants as contrasted to the products. An effective catalyst for the hydrolysis of an ester would be one which irreversibly adsorbed ester and water and rapidly desorbed alcohol and acid. Over various catalysts one might obtain yields of ester varying from 0 to 100 per cent, depending upon the characteristics of the catalyst involved.

The last step to be performed by a good catalyst is to give up the product at the right time or stage. Sometimes it is possible to modify a catalyst so that it will desorb a product at an intermediate stage of the reaction. For example, methanol is oxidized by air to give ultimately carbon dioxide and water:



Over iron oxide at 370° the reaction runs to completion, but if molybdenum oxide is incorporated with the iron oxide, the first product of oxidation, formaldehyde, is desorbed. The iron-molybdenum oxide catalyst thus makes possible a process by which methanol is oxidized almost quantitatively to formaldehyde.⁵⁴

The failure of a hydrogenation catalyst to desorb a product sufficiently rapidly may result in poisoning—i.e., covering of the catalyst by the product—or interaction between molecules of the desired product still adsorbed on the catalyst. There is also danger that, if the desired product is not quickly desorbed, it may react further with hydrogen as illustrated above in the hydrogenation of an ester to a hydrocarbon at 330°.

⁵⁴ Meharg and Adkins, U. S. pat., 1,913,404-5 (June, 1933); Adkins and Peterson *J. Am. Chem. Soc.*, **53**, 1512 (1931).

There is a balance or competition between the adsorption of each of the compounds present, e.g., hydrogen, hydrogen acceptor, solvent, and products. Often a high pressure of hydrogen will minimize the poisoning effect of the products as well as their tendency to interact while on the surface of the catalyst, since it will increase the proportion of the surface covered by hydrogen, which thus replaces other adsorbates. In a similar way high pressures of hydrogen minimize or eliminate the effect of small amounts of "poisons" present in the reaction mixture. It is probably for this reason that less care need be taken in the purification of compounds for hydrogenation at pressures of 100 to 300 atmospheres than with platinum or palladium at 1 to 3 atmospheres.

The solvent or reaction medium as well as the hydrogen, hydrogen acceptor, and product are no doubt adsorbed by the catalyst and so may play a role in determining the extent or course of the reactions. Solvents may be beneficial only because they facilitate the dispersion of the catalyst and the contact of the three essential materials, hydrogen, catalyst, and organic compound. However, in some cases, a more specific role is played by the solvent. For example, in the presence of ethanol only two of the three phenyl groups in triphenylmethane are hydrogenated, whereas in the presence of methyleyclohexane the hydrogenation goes to completion.⁵⁵ In the hydrogenation of amides and lignin, dioxane appears to be particularly beneficial in facilitating reaction.

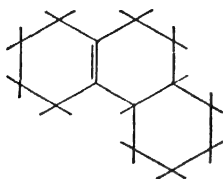
REDUCTION OF VARIOUS FUNCTIONAL GROUPS

Alkenes

The catalytic addition of hydrogen is the most general reaction of the carbon to carbon double bond. Many compounds containing the linkage $>C=C<$ will not show addition reactions with any other reagent but will add hydrogen under the influence of nickel. It seems safe to say that over 99 per cent of all the known compounds containing the alkene linkage will add hydrogen at temperatures from 0° to 275°. The olefinic linkage is one of the groups most easily reduced. Any of the common catalysts may be used. The rate of hydrogenation and the severity of conditions required vary with substitution at the alkene carbons. The simple alkenes such as ethylene and the amylenes react with hydrogen at room temperature and at pressures of hydrogen near one atmosphere in the presence of a catalyst. Even a trisubstituted ethylene $(C_6H_5)_2C=CHC_6H_5$ may be readily hydrogenated over

⁵⁵ Adkins, Zartman, and Cramer, *ibid.*, **53**, 1425 (1931).

Raney nickel at 25°* under a pressure of one hundred atmospheres of hydrogen.⁵⁶ However, a completely substituted ethylene such as in



where the double bond is common to two rings may be very resistant to hydrogenation. A temperature of 250° was required for the complete hydrogenation of the dodecahydrophenanthrene⁵⁷ whose formula is given above. A high-molecular-weight unsaturated compound, such as rubber, required a temperature as high as 275° to insure complete saturation. Unsaturated compounds having a conjugated system are likely to require more drastic conditions for hydrogenation than compounds of similar complexity but with isolated double bonds. The variation between cyclohexene (25°), furan (75°), benzene (125°), pyridine (175°), and pyrrole (225°) with respect to ease of hydrogenation over nickel is indicated by the figures given in parentheses. These are mere approximations, the exact figures depending upon the activity of the catalyst and the purity of the hydrogen acceptors. However, conjugation does not necessarily retard hydrogenation, for compounds of the type $RCH=C(CO_2C_2H_5)_2$ are rapidly hydrogenated over Raney nickel at room temperature.⁵⁸

Temperature; pressure of hydrogen; purity of compound; and amount, activity, and dispersion of catalyst are interdependent variables so that it is impossible to assign any definite conditions of temperature and pressure of hydrogen under which a given type of structure will be hydrogenated. Though nickel may often be used at pressures of a few atmospheres, in general pressures of the order of 100 to 200 atmospheres are more satisfactory. Under these conditions most isolated alkene linkages and furans will be hydrogenated below 150°.

Because of the mildness of the conditions necessary for the hydro-

* Hydrogenation has been accomplished in many cases under even milder conditions. The discussion in this section is not based upon the minimum conditions under which the reaction of hydrogen has been observed, but rather upon the conditions under which the reaction may be carried out on a preparational scale to give high yields of the saturated compound.

⁵⁶ Zartman and Adkins, *ibid.*, **54**, 1668 (1932).

⁵⁷ Durland and Adkins, *ibid.*, **60**, 1501 (1938).

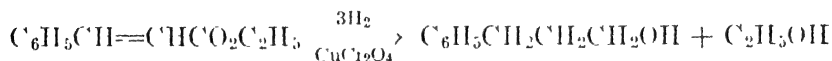
⁵⁸ Wojcik and Adkins, *ibid.*, **56**, 2424 (1934).

genation it is often feasible to hydrogenate the >C=C< preferentially. For example, it is possible to reduce styrene to ethylbenzene.⁵⁹ At 175° and 100 atmospheres pressure complete reduction to ethyl cyclohexane may be effected in the presence of Raney nickel or nickel on kieselguhr.⁵⁶

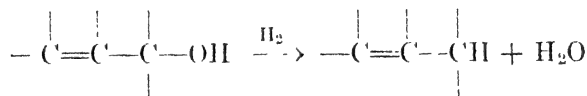


Unsaturated esters,⁶⁰ acids, and amides and derivatives of furan, benzene, pyrrole, and pyridine can usually be hydrogenated preferentially at the >C=C< linkage. Unsaturated ketones such as mesityl oxide, $(\text{CH}_3)_2\text{C=CHCOCH}_3$, or heptylidene acetoacetic ester, $\text{CH}_3\text{COC(=C}_7\text{H}_{14})\text{CO}_2\text{C}_2\text{H}_5$, can be hydrogenated over nickel to isobutyl methyl ketone and heptyl acetoacetic ester, respectively, but in other cases the ketone group is hydrogenated under the same conditions and at the same time as the alkene linkage.⁵⁸

Copper chromite also catalyzes the reduction of alkenes at 150-175°. If some other group in the molecule is also to be reduced which requires copper chromite as the catalyst, it is possible to effect both reductions in one operation. For example, ethyl cinnamate may be converted to 3-phenyl-1-propanol.⁶¹



One of the more important structural limitations upon the use of catalytic hydrogenation of olefinic linkages is the readiness with which the following type of reaction occurs:



If the double bond is resistant to hydrogenation as in a benzenoid, pyridinoid, or pyrroloid nucleus then it serves to labilize the carbon to oxygen linkage with the resultant hydrogenolysis indicated above.

Practically every olefin which is known has been reduced to the corresponding saturated compound. Only a few typical examples are listed in Table I.

⁵⁹ Kern, Shriner, and Adams, *ibid.*, **47**, 1147 (1925).

⁶⁰ Cope and Hancock, *ibid.*, **60**, 2644 (1938); **61**, 776 (1939).

⁶¹ Folkers and Adkins, *ibid.*, **54**, 1145 (1932).

TABLE I*
HYDROGENATION OF ALKENES TO ALKANES

| Compound | Catalyst | | | Temperature, °C. | Pressure, atm. | Amt. of Com- pound, moles | Time, min. | Ref. |
|---|---------------------------|-------------|---------------------------|---------------------|-------------------|------------------------------------|---------------|------|
| | Type † | Amt., g. | Sol- vent | | | | | |
| $(\text{CH}_3)_2\text{C}=\text{CHCH}_3$ | PtO_2 | 0.1 | EtOH | 25 | 3 | 0.1 | 6 | 59 |
| $\text{C}_6\text{H}_5\text{CH}=\text{CH}_2$ | PtO_2 | 0.1 | EtOH | 25 | 3 | 0.1 | 9 | 59 |
| $(\text{C}_6\text{H}_5)_2\text{C}=\text{CH}_2$ | PtO_2 | 0.1 | EtOH | 25 | 3 | 0.1 | 10 | 59 |
| $\text{C}_6\text{H}_5\text{CH}=\text{CHC}_6\text{H}_5$ (<i>trans</i>). | PtO_2 | 0.1 | EtOH | 25 | 3 | 0.1 | 38 | 59 |
| $\text{C}_6\text{H}_5\text{CH}=\text{HC}_6\text{H}_5$ (<i>trans</i>). | PdO | 0.1 | EtOH | 25 | 3 | 0.1 | 69 | 59 |
| $\text{C}_6\text{H}_5\text{CH}=\text{CHC}_6\text{H}_5$ (<i>trans</i>). | $\text{Ni}(k)$ | 2.0 | C_7H_{14} | 20 | 3 | 0.1 | 80 | 56 |
| $\text{C}_6\text{H}_5\text{CH}=\text{CHC}_6\text{H}_5$ (<i>trans</i>). | $\text{Ni}(k)$ | 2.0 | C_7H_{14} | 20 | 30 | 0.1 | 35 | 56 |
| $\text{C}_6\text{H}_5\text{CH}=\text{HC}_6\text{H}_5$ (<i>trans</i>). | $\text{Ni}(k)$ | 2.0 | C_7H_{14} | 20 | 90 | 0.1 | 15 | 56 |
| $(\text{C}_6\text{H}_5)_2\text{C}=\text{C}(\text{C}_6\text{H}_5)_2$ | PtO_2 | 0.2 | EtOH | 25 | 3 | 0.02 | 360 | — |
| $(\text{C}_6\text{H}_5)_2\text{C}=\text{C}(\text{C}_6\text{H}_5)_2$ | CuCr_2O_4 | 1.0 | C_7H_{14} | 150 | 100 | 0.04 | 15 | 56 |
| $\text{CH}_2=\text{CH}(\text{CH}_2)_8\text{CO}_2\text{H}$ | PtO_2 | 0.1 | EtOH | 25 | 3 | 0.1 | 1.5 | 59 |
| $\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CH}_2\text{CH}=\text{CH}_2$ | PtO_2 | 0.1 | EtOH | 25 | 3 | 0.1 | 3.5 | 59 |
| $\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{CH}_3$ | PtO_2 | 0.1 | EtOH | 25 | 3 | 0.1 | 10 | 59 |
| $\text{C}_6\text{H}_5\text{CH}=\text{CHCOOH}$ (<i>trans</i>). | CuCr_2O_4 | 2.0 | C_7H_{14} | 175 | 100 | 0.24 | 20 | 62 |

* The data in this table and subsequent tables in this chapter are taken from specific experiments by many different investigators. Since there are so many variable factors no significance should be attached to small differences. The data are intended to serve as a guide to illustrate the general discussion.

† In this and all subsequent tables the nature of the catalyst is indicated by the following abbreviations:

PtO_2 = platinum oxide catalyst, p. 781

$\text{Pt}(\text{Coll})$ = colloidal platinum catalyst, p. 783

PdO = palladium oxide catalyst, p. 786

$\text{Pd}(\text{BaSO}_4)$ = palladium supported on barium sulfate, p. 786.

$\text{Pd}(\text{C})$ = palladium supported on Norite, p. 786

$\text{Ni}(R)$ = nickel prepared from Raney nickel-aluminum alloy, p. 788

$\text{Ni}(k)$ = nickel supported on kieselguhr, p. 788

CuCr_2O_4 = copper chromite catalyst, p. 788

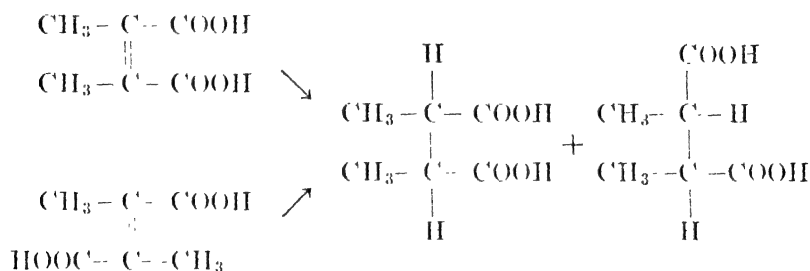
The *cis* forms of ethylenic compounds are usually more rapidly hydrogenated than the *trans* isomers. For example, Paal⁶³ has shown that the *cis* forms of the following compounds are more rapidly reduced than the *trans* forms.

⁶² Adkins and Connor, *ibid.*, **53**, 1091 (1931).

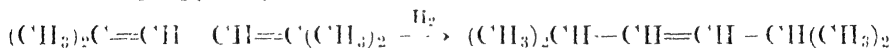
⁶³ Paal and Schiedewitz, *Ber.*, **60**, 1221 (1927); **63**, 766 (1930).

| <i>cis</i> | <i>trans</i> |
|---------------------------------------|---|
| Maleic | Fumaric |
| Oleic | Elaidic |
| Crotonic | Isocrotonic |
| Stilbene | Isostilbene |
| <i>cis</i> - <i>o</i> -Ethoxycinnamic | <i>trans</i> - <i>o</i> -Ethoxycinnamic |
| Erucic | Brassicic |

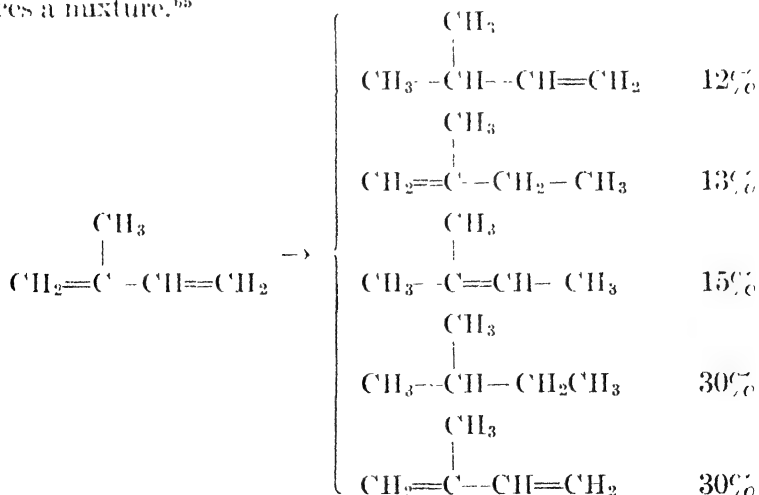
The catalytic reduction of tetrasubstituted olefins, such as dimethylfumaric and dimethylmaleic acids, leads to the production of diastereoisomeric products. A study of the hydrogenation of the sodium salts of the above acids has shown that by proper choice of experimental conditions either *cis* or *trans* addition of hydrogen may be made to occur.⁶⁴



Similar results were obtained with 2,3-diphenyl-2-butene. Catalytic hydrogenation in the presence of platinum black or diisobutyl leads to *sym*-diisopropylethylene.



Isoprene upon treatment with one mole of hydrogen and platinum black produces a mixture.⁶⁵



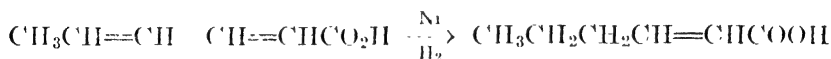
⁶⁴ Ott, Schröter, and Behr, *Ber.*, **61**, 2124 (1928).

⁶⁵ Lebedev and Yakubchik, *J. Chem. Soc.*, 823, 2190 (1928).

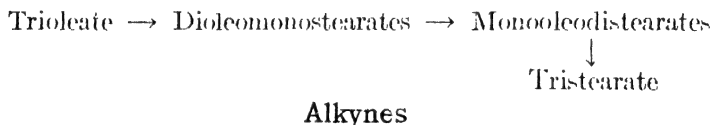
1,3-Butadiene, piperylene, and diisopropenyl also yield similar mixtures.

Olefinic bonds which are conjugated with a keto or carboxyl group are reduced more slowly than isolated double bonds.

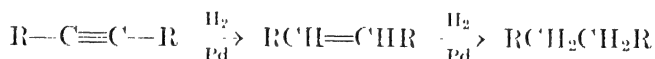
The γ,δ -double bond in sorbic acid is more readily reduced than the α,β -conjugated bond. Although a mixture of hexenoic acids is obtained, the α,β -predominates.⁶⁶



The hydrogenation of unsaturated glycerides proceeds in an interesting stepwise manner. Reduction of glyceryl trilinoleate with nickel on kieselguhr and hydrogen leads to nearly complete conversion to glyceryl trioleate (*cis* and *trans* forms) before the latter are further hydrogenated. The production of the completely saturated fat, glyceryl tristearate, does not occur until the final stages of the hydrogenation. Moreover, triolein disappears more rapidly than the tristearate is produced. These results are interpreted as indicating that only one double bond of the triolein is reduced during one contact with the catalyst.^{67a} The reduction sequence is probably:



Acetylenic compounds are readily reduced to the saturated alkane derivatives. This reaction is of little synthetic interest but is useful for structure proof. By using small amounts of catalyst and hydrogen at about 1 atmosphere pressure, and by interrupting the hydrogenation when one mole of hydrogen is absorbed, it is possible to obtain 70 to 90 per cent yields of the corresponding ethylenic derivative.

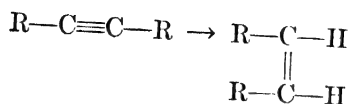


Recent work by Campbell and O'Connor^{67b} has shown that with palladium and Raney nickel the hydrogenation of a triple bond proceeds virtually to completion before the olefinic linkage begins to be reduced. Paul and Hilly^{67c} and Thompson and Wyatt^{67d} have obtained selective hydrogenation of certain alkynes to alkenes over an iron catalyst.

⁶⁶ Farmer and Galley, *ibid.*, 687 (1933); *Ann. Repts. Chem. Soc. (London)*, **30**, 143 (1933).

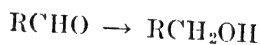
^{67(a)} Hilditch and Jones, *J. Chem. Soc.*, 805 (1932). (b) Campbell and O'Connor, *J. Am. Chem. Soc.*, **61**, 2897 (1939). (c) Paul and Hilly, *Bull. soc. chim.*, [5] **6**, 218 (1939). (d) Thompson and Wyatt, *J. Am. Chem. Soc.*, **62**, 2555 (1940).

Bourguel⁶⁸ has shown that eleven acetylenic compounds uniformly produce the *cis*-ethylenic derivative when treated with hydrogen in the presence of colloidal palladium stabilized by starch



Aldehydes

Both aliphatic and aromatic aldehydes are rapidly reduced to the corresponding alcohol.



When platinum is used, it is necessary to add a trace of a ferrous salt in order to obtain complete reduction.⁶⁹ Some typical reductions are shown in Table II.

TABLE II
REDUCTION OF ALDEHYDES TO ALCOHOLS

| Aldehyde | Catalyst | | Solvent | Temperature, °C. | Pressure, atm. | Moles of Compound | Time, min. | Ref. |
|---|----------------------------------|------|--------------------------------|------------------|----------------|-------------------|------------|------|
| | Type | Amt | | | | | | |
| C ₆ H ₅ CHO | PtO ₂ | 0.23 | Alc (Fe ⁺⁺) | 25 | 3 | 0.2 | | |
| C ₆ H ₅ CHO | PdO | 0.23 | Alc. | 25 | 3 | 0.2 | 20 | 69 |
| C ₆ H ₅ CHO | Pd(BaSO ₄) | 2.5 | HOAc | 25 | 1 | 0.1 | 21 | 28 |
| C ₆ H ₅ CHO | CuCr ₂ O ₄ | 5.0 | C ₇ H ₁₄ | 180 | 150 | 0.7 | 57 | 70 |
| CH ₃ (CH ₂) ₅ CHO | PtO ₂ | 0.23 | Alc (Fe ⁺⁺) | 25 | 3 | 0.2 | 1 | 62 |
| CH ₃ (CH ₂) ₆ CHO | Ni(R) | 6.0 | C ₇ H ₁₄ | 150 | 100 | 2.5 | 30 | 69 |
| CH ₃ CHOHCH ₂ CHO | Ni(k) | 2.0 | C ₇ H ₁₄ | 125 | 100 | 1.0 | 240 | 62 |
| Glucose | Ni(k) | 2.0 | H ₂ O | 150 | 100 | 0.1 | 60 | 71 |
| | | | | | | | 150 | 72 |

Unsaturated aldehydes are completely reduced to the saturated alcohols unless special conditions are used to obtain selective reduction. In order to reduce an unsaturated aldehyde to an unsaturated alcohol with platinum, a trace of ferrous salt is added to promote reduction of the aldehyde group and also a trace of zinc acetate to inhibit the reduc-

⁶⁸ Bourguel, *Bull. soc. chim.*, [4] **45**, 1067 (1929); cf. Salkind and Teterin, *J. Russ. Phys. Chem. Soc.*, **61**, 1751 (1929).

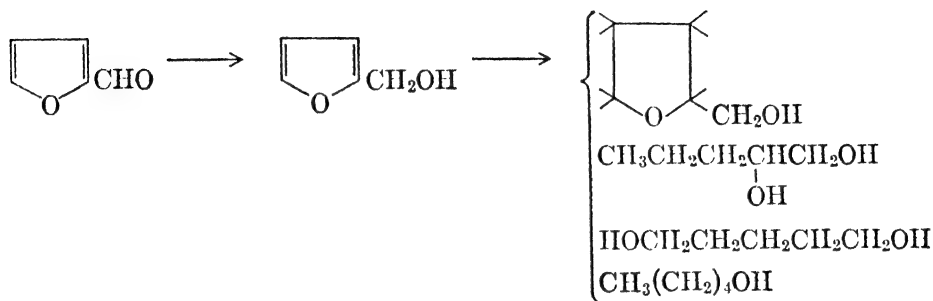
⁶⁹ Carothers and Adams, *J. Am. Chem. Soc.*, **45**, 1071 (1923); **46**, 1680 (1924).

⁷⁰ Rosenmund and Jordan, *Ber.*, **58**, 160 (1925).

⁷¹ Winans and Adkins, *J. Am. Chem. Soc.*, **55**, 4167 (1933).

⁷² Covert, Connor, and Adkins, *ibid.*, **54**, 1651 (1932).

The catalytic reduction of furfural over platinum oxide leads first to the formation of furfuryl alcohol.⁷⁵ Further reduction produces a mixture of tetrahydrofurfuryl alcohol, pentanediol-1,2, pentanediol-1,5, and *n*-amyl alcohol. Reduction of alkyl furyl carbinols⁷⁶ likewise produces a corresponding series of reduction products.



Furfural is rapidly and almost quantitatively hydrogenated to furfuryl alcohol over copper chromite at 135-160° under 50 to 150 atmospheres of hydrogen. When nickel was used as a catalyst the furfuryl alcohol was contaminated with tetrahydrofurfuryl alcohol.⁷⁷

Ketones

The carbonyl group of ketones is reduced more slowly at room temperature over platinum and palladium catalysts than in the case of aldehydes. With nickel a temperature of 100° to 150° is usually necessary although Raney nickel induced the hydrogenation of acetone and acetoacetic ester⁷⁸ at room temperature. A temperature of 100° to 175° under 50 to 150 atmospheres of hydrogen is usually advisable if copper chromite is to be used.

If the carbonyl group is attached to a benzene nucleus the same care must be taken as with the aldehydes to prevent the first-formed secondary alcohol group being converted to a methylene group. If the carbonyl is attached to a pyrrole nucleus it has proved impossible to stop the hydrogenation of the carbonyl at the carbinol stage.

The catalytic hydrogenation of ketones is a process in which side reactions are seldom encountered and the yields of secondary alcohols obtained are well above 90 per cent for simple aliphatic ketones. Even with the aryl ketones yields of the order of 70 to 80 per cent are usually obtained. Examples are given in Table III.

⁷⁵ Kaufmann and Adams, *ibid.*, **45**, 3029 (1923).

⁷⁶ Pierce and Adams, *ibid.*, **47**, 1098 (1925).

⁷⁷ Connor, Folkers, and Adkins, *ibid.*, **53**, 1091 (1931).

⁷⁸ Covert and Adkins, *ibid.*, **54**, 4116 (1932).

TABLE III
 REDUCTION OF KETO GROUPS TO SECONDARY ALCOHOLS

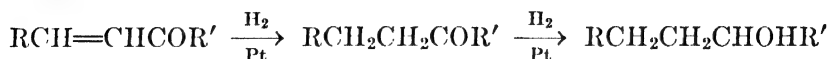
| Ketone | Catalyst | | Solvent | Temperature, °C. | Pressure, atm. | Moles of Com- pound | Time, min. | Ref. |
|---------------------------|----------------------------------|-------------|----------------------------------|---------------------|-------------------|------------------------------|---------------|------|
| | Type | Amt., g. | | | | | | |
| Acetone | Ni(k) | 2 | | 125 | 100 | 1 0 | 13 | 72 |
| Acetophenone | Ni(R) | 4 | C ₂ H ₅ OH | 110 | 100 | 0 4 | 10 | 79 |
| Benzophenone . . | Ni(k) | 1 | C ₂ H ₅ OH | 160 | 100 | 0 1 | 60 | 79 |
| <i>d</i> -Camphor | CuCr ₂ O ₄ | 6 | C ₂ H ₅ OH | 120 | 150 | 0 5 | 60 | 80 |
| Benzoin | Ni(k) | 2 | C ₂ H ₅ OH | 125 | 100 | 0 2 | 60 | 62 |
| Fructose | Ni(k) | 2 | H ₂ O | 150 | 100 | 0 1 | 150 | 72 |
| Ethyl aceto- acetate | Ni(k) | 2 | C ₂ H ₅ OH | 125 | 100 | 0 4 | 120 | 81 |
| Ethyl levulinate | Ni(k) | 4 | C ₂ H ₅ OH | 100 | 100 | 0 2 | 80 | 72 |

β -Keto esters should be hydrogenated in an alcohol solution as otherwise a condensation product is obtained. For example, acetoacetic esters when hydrogenated without a solvent gave more than a 30 per cent yield of $\text{CH}_3\text{CHOHCH}_2\text{COOCH}(\text{CH}_3)\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$, while in alcohol, the yield of $\text{CH}_3\text{CHOHCH}_2\text{CO}_2\text{C}_2\text{H}_5$ was almost quantitative.⁸¹

Copper chromite and nickel for most ketones are equally satisfactory as catalysts. Nickel is usually active at a somewhat lower temperature, but copper chromite is more selective in its action as illustrated in the hydrogenation of furfural.

β -Diketones of the type $\text{RCOCH}_2\text{COCH}_3$ may be selectively hydrogenated to keto alcohols of the type $\text{RCOCH}_2\text{CHOHCH}_3$ by limitation of the amount of hydrogen allowed to react. A more complete hydrogenation gives glycols. Certain substituted β -diketones such as $\text{C}_6\text{H}_5\text{COCH}(\text{CH}_2\text{C}_6\text{H}_5)\text{COCH}_3$ are cleaved by hydrogen so that about one-half of the diketone is converted by hydrogenolysis to benzaldehyde, 1-phenylbutanone-3, and 1,3-diphenylpropanone-1.⁸²

The olefinic linkage is reduced more rapidly than the keto grouping; hence unsaturated ketones, such as mesityl oxide, benzalacetone, and benzalacetophenone are reduced first to the saturated ketones and then to the alcohols.



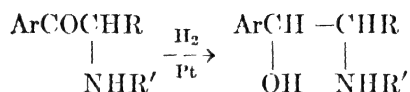
⁷⁹ Adkins *et al.*, unpublished work.

⁸⁰ Bowden and Adkins, *J. Am. Chem. Soc.*, **56**, 689 (1934).

⁸¹ Adkins, Connor, and Cramer, *ibid.*, **52**, 5192 (1930).

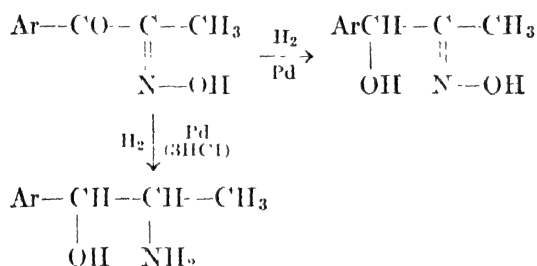
⁸² Sprague and Adkins, *ibid.*, **56**, 2669 (1934); Stutsman and Adkins, *ibid.*, **61**, 3303 (1939).

Catalytic reduction with platinum or palladium has been shown to be an effective method for the synthesis of homologs of ephedrine. The pure hydrochlorides of the amino ketones, dissolved in alcohol, are readily reduced to the amino alcohols with platinum oxide⁸³ and hydrogen at 3 atmospheres.

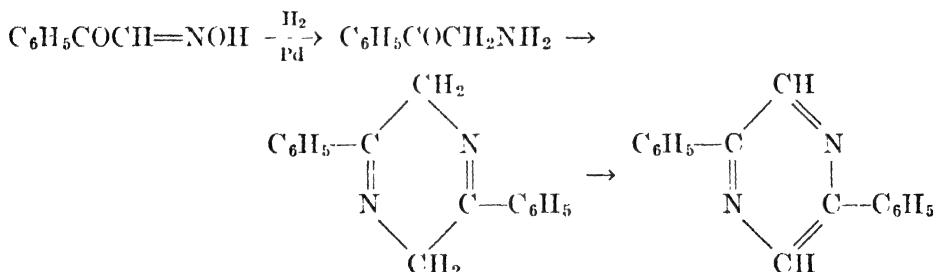


Although two diastereoisomeric forms of the product are possible only one form was obtained. Thus, when Ar is phenyl, and R and R' are methyl groups, catalytic reduction produces *dl*-ephedrine and not pseudo-ephedrine.

Hartung⁸⁴ has found that a palladium-Norite catalyst and hydrogen reduced α -oximino ketones to the α -hydroxyoximes. However, in the presence of three equivalents of hydrochloric acid the α -hydroxy amines



were produced. When α -oximinoacetophenone is reduced over palladium⁸⁴ or nickel,⁸⁵ the amino ketone is the first product; this undergoes self-condensation and dehydrogenation to produce diphenylpyrazine.



⁸³ Hyde, Browning, and Adams, *ibid.*, **50**, 2287 (1928).

⁸⁴ Hartung, *ibid.*, **50**, 3370 (1928); **53**, 2248 (1931); Hartung and Munch, *ibid.*, **51** 2262 (1929); Hartung, Munch, Deakert, and Crossley, *ibid.*, **52**, 3317 (1930).

⁸⁵ Brown, Durand, and Marvel, *ibid.*, **58**, 1594 (1936).

Halogen Compounds

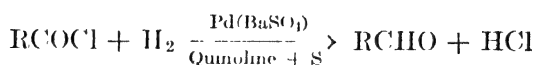
Busch and Stöve³⁵ have shown that the halogen in many types of compounds may be quantitatively removed by treating an alcoholic potassium hydroxide solution of the substance at room temperature with a palladium-calcium carbonate catalyst and hydrogen at 1 atmosphere. The method has been proposed for the quantitative determination of halogen in organic compounds. Some typical examples are shown in Table IV.

TABLE IV
REPLACEMENT OF HALOGEN BY HYDROGEN³⁵

| Compound | Catalyst | | Solvent | Temperature, °C. | Pressure, atm. | Amt. of Compound, g. | Time, hr. |
|------------------------------|------------------------|----------|----------|------------------|----------------|----------------------|-----------|
| | Name | Amt., g. | | | | | |
| Ethylene bromide . . . | Pd(CaCO ₃) | 1 | Ale. KOH | 20 | 1 | 0.21 | 1.0 |
| Chloroacetic acid . . . | Pd(CaCO ₃) | 1 | Ale. KOH | 20 | 1 | 0.28 | 3.0 |
| Benzal chloride | Pd(CaCO ₃) | 1 | Ale. KOH | 20 | 1 | 0.23 | 0.8 |
| Tolane tetrachloride . . | Pd(CaCO ₃) | 1 | Ale. KOH | 20 | 1 | 0.19 | 1.0 |
| Bromobenzene | Pd(CaCO ₃) | 1 | Ale. KOH | 20 | 1 | 0.26 | 0.33 |
| 2,4,6-Tribromophenol | Pd(CaCO ₃) | 1 | Ale. KOH | 20 | 1 | 0.18 | 0.45 |
| <i>m</i> -Bromobenzoic acid. | Pd(CaCO ₃) | 1 | Ale. KOH | 20 | 1 | 0.20 | 0.15 |

With platinum oxide as a catalyst and alcohol as the solvent, a temperature of 50–70°, and hydrogen at 3 atmospheres, Brown, Durand, and Marvel⁸⁵ have shown that aromatic halogen compounds are dehalogenated and hydrogenated to the saturated cycloparaffins in 70 to 95 per cent yields.

Rosenmund^{86, 87, 88, 89a} has developed a useful method for the synthesis of aldehydes by replacing the halogen of an acyl chloride by hydrogen in the presence of palladium catalysts on barium sulfate or kieselguhr. In order to prevent reduction of the aldehyde, a poison, "sulfurized quinoline" or thioquinanthrene is added. The reductions are usually carried



⁸⁶ Rosenmund and Zetzsche, *Ber.*, **54**, 425 (1921).

⁸⁷ Rosenmund, Zetzsche, and Flutsch, *Ber.*, **54**, 2888 (1921).

⁸⁸ Rosenmund, Zetzsche, and Enderlin, *Ber.*, **55**, 609 (1922).

^{89a} Rosenmund, Zetzsche, and Weiler, *Ber.*, **56**, 1481 (1923).

out by passing hydrogen through a boiling toluene or xylene solution of the acid chloride in which the catalyst is suspended.^{89b} Some typical examples are shown in Table V.

TABLE V
ALDEHYDES FROM ACID CHLORIDES

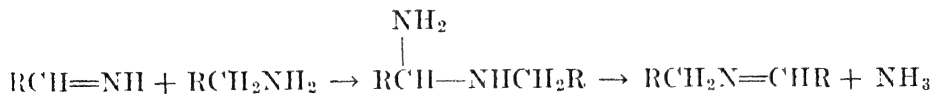
| Compound | Catalyst | | Amt Sulfurized Quinoline, mgr. | Solvent | Bath Temp., °C | Amount of Compound, g | Time, hr. | Ref. |
|---------------------------|---------------|--------|--------------------------------|---------|----------------|-----------------------|-----------|------|
| | Name | Amt, g | | | | | | |
| $C_6H_5CH_2COCl$ | $Pd(BaSO_4)$ | 2.0 | 10 | Toluene | 115 | 2.3 | 4.0 | 86 |
| $p-O_2NC_6H_4COCl$ | $Pd(\lambda)$ | 0.5 | 10 | Xylene | 150 | 3.0 | 2.5 | 82 |
| $m-C_6H_4(COCl)_2$ | $Pd(\lambda)$ | 0.2 | 2 | Xylene | 150 | 2.0 | 4.0 | 87 |
| $p-C_6H_4(COCl)_2$ | $Pd(\lambda)$ | 0.5 | 6 | Xylene | 150 | 20 | 32.0 | 87 |
| $ClCO(CH_2)_6COCl$ | $Pd(\lambda)$ | 0.2 | 2 | Xylene | 150 | 1 | 6 | 87 |
| $ClCO(CH_2)_8COCl$ | $Pd(\lambda)$ | 1.0 | 1 | Xylene | 150 | 19 | 15 | 88 |
| $C_6H_5OCH_2COCl$ | $Pd(BaSO_4)$ | 0.7 | 15 | Xylene | 133 | 2 | 3.5 | 89 |
| $\alpha-ClC_6H_4CH_2COCl$ | $Pd(BaSO_4)$ | 0.7 | 25 | Xylene | 125 | 1 | 1.2 | 89 |

Nitriles

The hydrogenation of nitriles in neutral solution results in the formation of a mixture of primary and secondary amines. The reduction apparently proceeds in a stepwise fashion through the aldimine. The



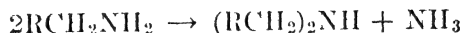
aldimine reacts with the primary amine in the same fashion as an aldehyde, leading to the Schiff's base



which then undergoes further reduction to the secondary amine.^{90, 91}



At temperatures above about 160° the primary amine may also lose ammonia to produce the secondary amine.⁹¹



^{89b} *Org. Syn.*, **21**, 84, 110 (1941).

⁹⁰ von Braun, Blessing, and Zobel, *Ber.*, **56**, 1988 (1923).

⁹¹ Winans and Adkins, *J. Am. Chem. Soc.*, **54**, 306 (1932).

When platinum oxide is the catalyst the percentage of primary amine may be increased by using glacial acetic acid as the solvent. With acetic anhydride as the solvent, yields up to 88 per cent of the acetylated primary amine may be obtained.⁹² High yields of the primary amine may be obtained by using palladium-Norite catalyst⁹³ and adding one equivalent of hydrochloric acid to the alcohol used as a solvent.

If nickel is the catalyst, the above modifications cannot be used since acids attack the finely divided nickel. In order to increase the yield of primary amines when nickel is the catalyst it is desirable to carry out the reduction as rapidly as possible and to dissolve some anhydrous ammonia in the solvent in order to repress the reaction of the aldimine with the already formed primary amine.^{91, 94, 95} In general, the hydrogenation of a nitrile over nickel should be carried out at 100° to 150°. The yield of primary amine should then be 70 to 90 per cent. Some typical reduction data on nitriles are given in Table VI.

TABLE VI
REDUCTION OF NITRILES

| Compound | Catalyst | | Solvent | Temp., °C | Pressure, atm | Moles of Compound | Time, hr. | Composition of Product | | Ref. |
|-----------------------|------------------------|---------|-------------------|-----------|---------------|-------------------|-----------|---------------------------------|-----------------------------------|------|
| | Name | Am't, g | | | | | | C ₁ Primary Amine | C ₂ Secondary Amine | |
| Benzonitrile | PtO ₂ | 0.8 | Abs. alc. | 25 | 3 | 0.4 | 21 | 21 | 79 | 92 |
| Benzonitrile | PtO ₂ | 0.5 | HOAc | 25 | 3 | 0.4 | 7 | 62 | 38 | 92 |
| Benzonitrile | PtO ₂ | 0.45 | Ac ₂ O | 25 | 3 | 0.2 | 6 | 67 | . | 92 |
| <i>o</i> -Tolunitrile | PtO ₂ | 0.5 | Ac ₂ O | 25 | 3 | 0.2 | 10 | 94 * | . | 92 |
| <i>p</i> -Tolunitrile | PtO ₂ | 0.21 | Ac ₂ O | 25 | 3 | 0.2 | 5 | 88 * | . | 92 |
| Phenylacetoneitrile | PtO ₂ | 1.2 | Ac ₂ O | 25 | 3 | 0.2 | 22 | 63 * | . | 92 |
| Benzonitrile | Pd (C) | . | Ale + HCl | 25 | 1 | . | . | . | . | 93 |
| Benzonitrile | Pd(BaSO ₄) | . | HOAc | 25 | 1 | . | . | 80 | . | 96 |
| Phenylacetoneitrile | Pd(BaSO ₄) | . | HOAc | . | . | . | . | . | . | . |
| Valeronitrile | Ni (R) | 20 | + HCl | 25 | 1 | . | . | 73 | . | 96 |
| Benzonitrile | Ni (R) | 20 | . | 125 | 100 | 4.8 | 0.5 | 67 | 16 | 94 |
| Benzonitrile | Ni (R) | 20 | . | 150 | 100 | 5.3 | 0.3 | 75 | 19 | 94 |
| <i>o</i> -Tolunitrile | Ni (k) | 2 | . | 125 | 100 | 0.35 | 2.5 | 69 | . | 97 |

* As N-substituted acylamide

⁹² Carothers and Jones, *ibid.*, **47**, 3051 (1925).

⁹³ Hartung, *ibid.*, **50**, 3370 (1928).

⁹⁴ Schwoegler and Adkins, *ibid.*, **61**, 3499 (1939).

⁹⁵ Howk, U. S. pat., 2,166,151 (July 18, 1939) [*C. A.*, **33**, 8211 (1939)].

⁹⁶ Rosenmund and Pfankuch, *Ber.*, **56**, 2258 (1923).

⁹⁷ Adkins and Cramer, *J. Am. Chem. Soc.*, **52**, 4349 (1930).

Oximes

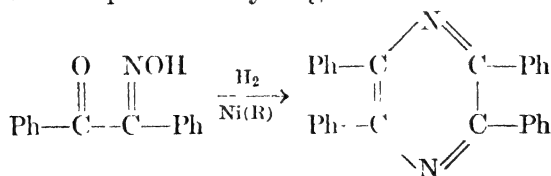
With oximes, as with nitriles, secondary amine formation may occur to a large extent when hydrogenation is carried out in neutral solvents. Hartung and his co-workers^{84, 93} have recommended the addition of three or more equivalents of hydrogen chloride to the alcoholic solution of the oxime and report high yields of the primary amine by hydrogenation under these conditions. Glacial acetic acid has also been used as a solvent. Hydrogenation of the oxime acetate may give a higher yield of the primary amine than hydrogenation of the free oxime.⁹⁶ The reduction of α -oximino ketones has been discussed under ketones (p. 807).

The oximino group reacts with hydrogen over nickel under milder conditions than other functional groups with the possible exception of certain alkenes and imines.⁹⁸ It is not unusual for the reaction of an oxime with hydrogen over Raney nickel to begin at room temperatures. Since the reaction is quite exothermic, the temperature of the bomb and contents frequently rises to 40° or 50° without any external heating. It is probably desirable in the use of Raney nickel with oximes to keep the temperature of the reaction mixture below 80°. This is especially important with α -oximino ketones, from which resinous products are formed at higher temperatures.

With the simple oximes the only side reaction of any consequence is the formation of secondary amines as in the case of the cyanides, i.e., through the interaction of primary amine and the intermediate imine.

There is a good deal of variation in the proportion of primary and secondary amines formed from different oximes. In some cases the yield of primary amine was almost quantitative, as from the oximes of benzophenone and camphor, while in one or two instances the yield of primary amine was as low as 40 to 42 per cent. It is probable that with a few exceptions the yield of primary amine can be held at least as high as 70 to 80 per cent, with 20 to 15 per cent of secondary amine.

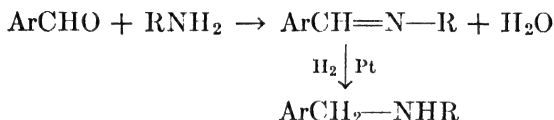
A number of oximino ketones and oximino esters are readily hydrogenated, but open-chain amines are not obtained because the amino ketone or amino ester just formed reacts with the formation of a pyrazine or pyrrolidone.^{71, 98} For example, the monoxime of benzil gave a 42 per cent yield of tetraphenylpyrazine when hydrogenated over Raney nickel under 150 atmospheres of hydrogen at 70 to 90°.



⁹⁸ Winans and Adkins, *ibid.*, **55**, 2051 (1933).

Aldimines and Ketimines

Aromatic aldehydes condense with primary amines to produce aldimines or Schiff bases. These may be hydrogenated at 25° and 3 atmospheres pressure in the presence of platinum oxide to produce the secondary amines in good yield.⁹⁹ Buck¹⁰⁰ has described the synthesis of



a series of substituted di-(β -phenylethyl)-amines and benzyl β -phenylethylamines by this method.

Since aliphatic aldehydes condense with aryl amines to produce polymeric condensation products it is usually not possible to obtain the Schiff bases. However, by treating an alcoholic solution of a primary aryl amine and an aliphatic aldehyde with hydrogen and Raney nickel in the presence of sodium acetate it is possible to obtain 50–65 per cent yields of alkyl aryl amines.¹⁰¹

Hydrazones, Semicarbazones, Ketazines, Hydrazo, and Azo Compounds

Hydrazones and ketazines have also been hydrogenated by means of platinum, palladium, and nickel catalysts. The reduction may stop with the formation of the hydrazine or hydrazo compound or may continue by cleaving the nitrogen to nitrogen bond to form primary amines. Bailey and his co-workers,^{102, 103, 104, 105, 106, 107} who used Skita's colloidal platinum catalyst, report that the reduction is greatly facilitated by the presence of a quantity of hydrochloric acid sufficient to form the salt of the hydrazo compound which is formed. Table VII contains some typical examples.

The hydrogenation of semicarbazones to semicarbazides is successfully accomplished under the proper conditions. Bailey and his co-workers¹⁰⁴ have used a colloidal platinum catalyst prepared with gum arabic by Skita's method. Hydrochloric acid must be present for suc-

⁹⁹ Rupe and Hodel, *Helv. Chim. Acta.*, **6**, 878 (1923).

¹⁰⁰ Buck, *J. Am. Chem. Soc.*, **53**, 2192 (1931).

¹⁰¹ Emerson and Walters, *ibid.*, **60**, 2023 (1938); Emerson and Robb, *ibid.*, **61**, 3145 (1939).

¹⁰² Lochte, Bailey, and Noyes, *ibid.*, **43**, 2597 (1921).

¹⁰³ Lochte, Noyes, and Bailey, *ibid.*, **44**, 2556 (1922).

¹⁰⁴ Neighbors, Foster, Clark, Miller, and Bailey, *ibid.*, **44**, 1557 (1922).

¹⁰⁵ Harkins and Lochte, *ibid.*, **46**, 450 (1924).

¹⁰⁶ Schulze and Lochte, *ibid.*, **48**, 1030 (1926).

¹⁰⁷ Poth and Bailey, *ibid.*, **45**, 3001 (1923).

TABLE VII
REDUCTION OF HYDRAZONES AND KETAZINES

| Compound | Catalyst | | Solvent | Temp., °C. | Pres- sure, atm. | Amount of Com- pound, g. | Time, hr. | Products | Ref. |
|---|---------------------------|----------|--|---------------|------------------------|-----------------------------------|--------------|------------------------|------|
| | Type | Amt., g. | | | | | | | |
| $(\text{CH}_3)_2\text{C}=\text{N}-\text{NH}_2$ | Pt (coll.) | 1 | H_2O HCl | 45 | 2 | | | Isopropyl hydrazine | 103 |
| $(\text{CH}_3)_2\text{C}=\text{N}-\text{NHCH}(\text{CH}_3)_2$ | Pt (coll.) | 1 | H_2O HCl | 45 | 2 | | | Hydrazo compound | 103 |
| $\text{CH}_3\text{CH}=\text{N}-\text{NHC}_6\text{H}_5$ | Pt (coll.) | 5 | Ale. $\text{H}_2\text{O}(\text{HCl})$ | 25 | 3 | 25 | 3 | Hydrazo compound | 104 |
| $(\text{CH}_3)_2\text{C}=\text{N}-\text{NH}-\text{C}_6\text{H}_5$ | Pt (coll.) | 5 | Ale. $\text{H}_2\text{O}(\text{HCl})$ | 25 | 3 | | | Hydrazo compound | 104 |
| $(\text{CH}_3)_2\text{C}=\text{N}-\text{N}=\text{C}(\text{CH}_3)_2$ | Pt (coll.) | 1 | H_2O HCl | 45 | 2 | 25 | 4 | Hydrazo compound | 102 |
| C_6H_5 CH_3 $\text{C}=\text{N}-\text{N}=\text{C}$ C_6H_5 CH_3 | Pt (coll.) | 1 | H_2O HCl | 45 | 1 | | | Hydrazo compound | 106 |
| $\text{C}_6\text{H}_5\text{CH}=\text{N}-\text{N}=\text{CC}_6\text{H}_5$ C_6H_5 | Pd (BaSO_4) | | HOAc | 25 | 1 | 0.4 | 0.5 | Benzylamine | 96 |

cessful reduction. Taipale and Smirnov,¹⁰⁸ who have used the Löw-Willstätter platinum black catalyst, report successful reduction in neutral alcohol solutions but faster reduction in glacial acetic acid. Examples are tabulated in Table VIII. The yields of semicarbazides isolated ranged from 76–95 per cent.

TABLE VIII
SEMICARBAZONES TO SEMICARBAZIDES

| Compound Semicarbazone of | Catalyst | | Solvent | Temp., °C | Pres- sure, atm. | Amount of Com- pound, g | Time, hr. | Ref |
|------------------------------|------------|---------|------------------------------------|--------------|------------------------|-------------------------------|--------------|-----|
| | Type | Amt., g | | | | | | |
| Acetone | Pt (coll.) | 0.5 | 33% CH ₃ OH + HCl | 20 | 2-3 | 50 | 6 | 107 |
| Benzaldehyde . . . | Pt (coll.) | 0.5 | 33% CH ₃ OH + HCl | 20 | 2-3 | 25 | 2-5 | 107 |
| Camphor | Pt (coll.) | 1.0 | 33% CH ₃ OH + HCl | 20 | 2-3 | 10 | 20 | 107 |
| Carvomenthone . . | Pt (coll.) | 0.5 | 33% CH ₃ OH + HCl | 20 | 2-3 | 50 | 5 | 107 |
| Cyclohexanone . . | Pt (coll.) | 0.5 | 33% CH ₃ OH + HCl | 20 | 2-3 | 50 | 3 | 107 |
| Menthone | Pt (coll.) | 0.5 | 33% CH ₃ OH + HCl | 20 | 2-3 | 50 | 2-7 | 107 |
| Acetaldehyde . . . | Pt | 0.5 | HOAc | 20 | 1 | 5 | 3-5 | 108 |
| Propionaldehyde . . | Pt | 1.0 | CH ₃ OH | 18 | 1 | 2-9 | 12 | 108 |

Azobenzene is rapidly reduced by hydrogen and colloidal palladium at room temperature and 1 atmosphere pressure. If the reduction is stopped after one mole of hydrogen has been absorbed hydrazobenzene may be isolated. Further reduction yields aniline.¹⁰⁹



A few other azo compounds have been studied.^{96, 103}

¹⁰⁸ Taipale and Smirnov, *Ber.*, **56**, 1794 (1923).

¹⁰⁹ Skita, *Ber.*, **45**, 3312 (1912).

The nitrogen to nitrogen bond in azobenzene, diazoaminobenzene, the azo dyes, and phenylhydrazones is cleaved by hydrogen over nickel catalysts at 75–125°. The corresponding amines have been isolated in good yields.^{71, 91, 98}

Nitro Compounds

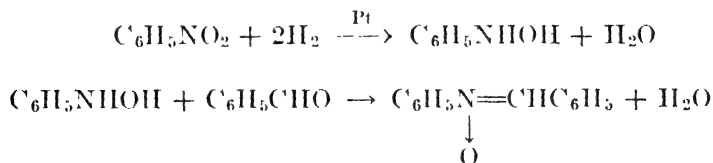
The nitro group undergoes catalytic reduction with great ease in the presence of the hydrogenation catalysts. The reaction is highly exothermic, and caution must be exercised in reducing nitro compounds to avoid excessively high temperatures. The amounts taken for reduction should be limited or the reducing bomb provided with an adequate cooling jacket.

Nitrobenzene, *m*-dinitrobenzene, *p*-nitrophenol, 3,3'-dinitrobiphenyl, and nitrocymene, for example, have been almost quantitatively reduced to the corresponding amines over Raney nickel at 75° to 125°. The hydrogenation of nitro compounds¹¹⁰ should be carried out in an alcoholic solution in order to maintain the homogeneity of the solution even after all the oxygen of the nitro group has been converted to water.

Raney nickel may react with a nitro compound with the formation of nickel oxide and azo and azoxy compounds.⁷⁸ Raney nickel has been used under 2 to 3 atmospheres pressure for the reduction of nitrobenzene arsonic acids¹¹¹ to the corresponding aminobenzene arsonic acids.

Both aromatic and aliphatic nitro compounds are smoothly reduced to the primary amine. When aliphatic nitro compounds are reduced in aqueous oxalic acid with hydrogen and palladium on barium sulfate the hydroxylamine oxalates may be obtained in 70–98 per cent yields.¹¹² Table IX contains some examples of the reduction of nitro compounds.

Nitro compounds may be reductively alkylated with aldehydes or ketones in the presence of hydrogen and a catalyst in order to produce nitrones, substituted hydroxylamines, secondary amines, and in a few cases tertiary amines. Reduction of a mixture of nitrobenzene and benzaldehyde with platinum and hydrogen yields the nitrone by reduction of the nitrobenzene to phenylhydroxylamine and condensation with the benzaldehyde.



¹¹⁰ Adkins, "Reactions of Hydrogen, etc.," p. 95, University of Wisconsin Press Madison (1937).

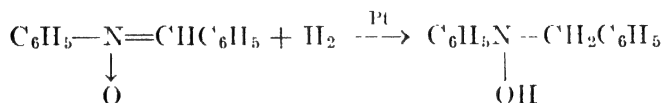
¹¹¹ Stevinson and Hamilton, *J. Am. Chem. Soc.*, **57**, 1298 (1935).

¹¹² Schmidt, Ascherl, and Mayer, *Ber.*, **58**, 2430 (1925).

TABLE IX
 REDUCTION OF NITRO COMPOUNDS

| Compounds | Catalyst | | Solvent | Temp., °C. | Pres- sure, atm. | Amount of Com- pound, moles | Time, min. | Product | Ref. |
|---|------------------------|--------------|--|---------------|------------------------|--------------------------------------|---------------|--|------|
| | Type | Am't., g. | | | | | | | |
| Nitrobenzene . . . | PtO ₂ | 0.2 | Ale. | 25 | 3 | 0.1 | 11 | Aniline | 113 |
| <i>o</i> -Nitrotoluene | PtO ₂ | 0.2 | Ale. | 25 | 3 | 0.1 | 11 | <i>o</i> -Toluidine | 113 |
| Methyl <i>p</i> -nitro- benzoate | PtO ₂ | 0.2 | Ale. | 25 | 3 | 0.1 | 11 | Methyl <i>p</i> - Aminoben- zoate | 113 |
| <i>p</i> -Nitrophenol . . | PtO ₂ | 0.2 | Ale. | 25 | 3 | 0.1 | 11 | <i>p</i> -Amino- phenol | 113 |
| <i>p</i> -Nitrochloro- benzene | PtO ₂ | 0.2 | Ale. | 25 | 3 | 0.1 | 11 | <i>p</i> -Chloro- aniline | 113 |
| Nitromethane . . | Pd(BaSO ₄) | 1 | H ₂ O + H ₂ C ₂ O ₄ | 25 | 1 | grams 6.1 | 8 | Substituted hydroxyl- amine oxalate | 112 |
| 1-Nitro-2- propanol . . . | Pd(BaSO ₄) | 2 | H ₂ O + H ₂ C ₂ O ₄ | 25 | 1 | 10.5 | 15 | | 112 |
| 1-Nitro-2- butanol | Pd(BaSO ₄) | 1.3 | H ₂ O + H ₂ C ₂ O ₄ | 25 | 1 | 6 | 7 | | 112 |
| 1-Nitro-2- octanol | Pd(BaSO ₄) | 1 | H ₂ O + H ₂ C ₂ O ₄ | 25 | 1 | 4.4 | 6 | | 112 |
| 1-Nitro-3- methyl-2 butanol | Pd(BaSO ₄) | 2 | H ₂ O + H ₂ C ₂ O ₄ | 25 | 1 | 6.5 | 20 | | 112 |
| 2-Nitro- propanediol- 1,3 | Pd(BaSO ₄) | 4.8 | H ₂ O + H ₂ C ₂ O ₄ | 25 | 1 | 4.8 | | Amine oxalate | 114 |

Further reduction of the nitronc produces the substituted hydroxyl-amine.¹¹⁵



Major¹¹⁶ found that reduction of *p*-nitrophenol in acetone solution with hydrogen and platinum produced *p*-hydroxy-N-isopropylaniline. Benzaldehyde and *p*-nitrophenol gave *p*-hydroxydibenzylaniline, and *p*-nitroaniline and acetone produced N,N-diisopropyl-*p*-phenylenediamine.

Yields of 31 to 96 per cent of N-alkyl arylamines may be obtained by dissolving the aromatic nitro compound in 95 per cent ethanol containing sodium acetate, adding the aliphatic or aromatic aldehyde and

¹¹³ Adams, Cohen, and Rees, *J. Am. Chem. Soc.*, **49**, 1093 (1927).

¹¹⁴ Schmidt and Wilkendorf, *Ber.*, **52**, 389 (1919).

¹¹⁵ Vavon and Cracjinovic, *Compt. rend.*, **187**, 420 (1928).

¹¹⁶ Major, *J. Am. Chem. Soc.*, **53**, 1901, 2803, 4373 (1931).

Raney nickel, and shaking the mixture with hydrogen at 3 to 4 atmospheres pressure.¹¹⁷

Aromatic Nuclei

Platinum black,^{12, 13} colloidal platinum¹¹⁸ and platinum oxide¹¹⁹ have been used as catalysts for the reduction of benzene and its derivatives. Adams and Marshall¹¹⁹ have found that glacial acetic acid is a better solvent for reduction of the aromatic nucleus than alcohol when platinum oxide is the catalyst. Generally the reductions required several hours. Brown, Durand, and Marvel⁸⁵ have found that addition of a small amount of hydrogen chloride to the alcoholic solution of the hydrocarbon promotes the reduction.

When platinum oxide is the catalyst aromatic amines are best reduced in the form of their hydrochlorides.¹²⁰ Also pyridine derivatives are reduced faster as their hydrochlorides in absolute alcohol solution than as the free bases.¹²¹ Heckel and Adams have prepared the amino cyclohexanols by reduction of aminophenols.¹²²

In Table X some examples of the reduction of aromatic compounds are given. It will be noted that many of these require considerable time for completion. It has been found that Raney nickel and nickel on kieselguhr will effect the reduction of aromatic nuclei much more rapidly.

Nickel is the most satisfactory catalyst for the hydrogenation of the benzenoid nucleus.¹²⁵ Benzene, toluene, other alkylbenzenes, phenol, cresols, and other alkylphenols, dihydric phenols, di- and triphenylmethanes, di-, tri-, and tetraphenylethanes, biphenyl, naphthalene, alkylnaphthalenes, and many other derivatives of benzene, naphthalene, anthracene, phenanthrene, etc., have been quantitatively saturated with hydrogen at temperatures from 100° to 200°. A hydrogen pressure of 100 to 300 atmospheres is desirable but not always necessary. The exact temperature and time required vary with the structure and purity of the compound and the activity of the catalyst. In most instances complete hydrogenation can be accomplished within a few hours at a maximum temperature of 200°.

The aromatic nucleus in such compounds as aniline, diphenylamine,

¹¹⁷ Emerson and Mohrman, *ibid.*, **62**, 69 (1940).

¹¹⁸ Skita and Meyer, *Ber.*, **45**, 3589 (1912); Skita and Schneek, *Ber.*, **55**, 144 (1922).

¹¹⁹ Adams and Marshall, *J. Am. Chem. Soc.*, **50**, 1970 (1928).

¹²⁰ Hiers and Adams, *ibid.*, **49**, 1099 (1927); *Ber.*, **59**, 162 (1926).

¹²¹ Hamilton and Adams, *J. Am. Chem. Soc.*, **50**, 2260 (1928).

¹²² Heckel and Adams, *ibid.*, **47**, 1712 (1925).

¹²³ Durland and Adkins, *ibid.*, **59**, 135 (1937); **60**, 1501 (1938).

¹²⁴ Signaigo and Adkins, *ibid.*, **58**, 709 (1936).

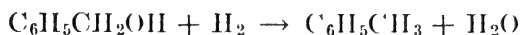
¹²⁵ Adkins, "Reactions of Hydrogen, etc.," pp. 56-62, University of Wisconsin Press Madison (1937).

TABLE X
 REDUCTION OF AROMATIC NUCLEI

| Compound | Catalyst | | Solvent | Temperature, °C. | Pressure, atm. | Amount of Compound, Moles | Time, hr. | Ref |
|--------------------------------|----------------------------------|---------|----------------------------------|---------------------|-------------------|------------------------------------|--------------|-----|
| | Type | Amt., g | | | | | | |
| Benzene | PtO ₂ | 0.2 | HOAc | 25 | 3 | 0.2 | 2 | 119 |
| Toluene | PtO ₂ | 0.2 | HOAc | 25 | 3 | 0.2 | 2.7 | 119 |
| <i>m</i> -Xylene | PtO ₂ | 0.2 | HOAc | 25 | 3 | 0.2 | 21 | 119 |
| Mesitylene | PtO ₂ | 0.2 | HOAc | 25 | 3 | 0.2 | 8.5 | 119 |
| Diphenylmethane | PtO ₂ | 0.2 | HOAc | 25 | 3 | 0.1 | 7.0 | 119 |
| Triphenylmethane | PtO ₂ | 0.8 | HOAc | 60 | 3 | 0.03 | 48 | 119 |
| Phenylacetic acid | PtO ₂ | 0.2 | HOAc | 25 | 3 | 0.1 | 5.5 | 119 |
| Cymene | PtO ₂ | 0.1 | Alc. HCl | 70 | 3 | 0.1 | 2.5 | 85 |
| Biphenyl | PtO ₂ | 0.1 | Alc. HCl | 70 | 3 | 0.1 | 10.0 | |
| Dimethylamine hydrochloride | PtO ₂ | 0.94 | Alc. | 50 | 3 | 0.1 | 0.5 | 120 |
| Diphenylamine hydrochloride | PtO ₂ | 0.25 | Abs. Alc | 50 | 3 | 0.1 | 2.0 | 120 |
| Pyridine hydro- chloride | PtO ₂ | 0.5 | Abs. Alc | 25 | 3 | 0.1 | 0.5 | 121 |
| Toluene | Ni(R) | 10 | | 175 | 100 | 1.3 | 0.1 | 55 |
| Mesitylene | Ni(L) | 3 | | 200 | 100 | 0.5 | 4 | 55 |
| Diphenylmethane | Ni(L) | 2 | C ₂ H ₅ OH | 150 | 100 | 0.1 | 7 | 55 |
| Biphenyl | Ni(L) | 2 | C ₂ H ₅ OH | 200 | 100 | 0.17 | 5 | 55 |
| Phenanthrene | Ni(R) | 5 | C ₂ H ₅ | 250 | 200 | 0.25 | 8 | 123 |
| Phenol | Ni(L) | 2 | | 150 | 100 | 0.5 | 3 | 97 |
| Diphenyl ether | Ni(L) | 2 | | 150 | 100 | 0.17 | 4 | 97 |
| Ethyl benzoate | Ni(L) | 8 | | 190 | 100 | 2.0 | 1 | 61 |
| Aniline | Ni(L) | 5 | | 175 | 100 | 1.0 | 9 | 97 |
| Quinoline | Ni(R) | 5 | | 200 | 100 | 0.41 | 1 | 97 |
| 1-Phenylpyrrole | CuCr ₂ O ₄ | 5 | | 210 | 150 | 0.10 | 2.5 | 124 |

triphenylamine, ethyl benzoate, diethyl phthalate, diethyl-1,1'-diphenate, ethyl γ -phenylpropionate, and 3-phenylpropanol-1 have also been hydrogenated under similar conditions. Aromatic ethers may likewise be hydrogenated fairly satisfactorily, although in many cases hydrogenolysis occurs. This type of reaction is discussed in more detail later in this chapter.

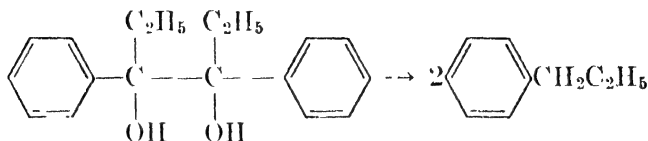
In general, it is not feasible to hydrogenate alcohols of the benzyl type since these compounds readily undergo hydrogenolysis to hydrocarbons.



Spielman and Docken¹²⁶ observed that the hydrogenolysis of a diaryl

¹²⁶ Spielman and Docken, unpublished results.

pinacol took another course. With copper chromite at 200° as the catalyst, *n*-propylbenzene was produced by hydrogenolysis of 3,4-diphenyl-3,4-hexanediol.



In general, copper chromite is not active for the hydrogenation of simple aromatic rings. For that reason it is very valuable as a catalyst for the partial hydrogenation of naphthalene,¹²⁷ phenanthrene,^{123, 128, 129} anthracene, quinoline,⁶² phenylpyrroles,¹²⁴ indoles,¹³⁰ and acridine.¹³⁰ For example, tetralin and dihydrophenanthrene are readily obtained by the partial hydrogenation of naphthalene and phenanthrene, respectively.

The pyridine ring may be hydrogenated over nickel under the same general conditions as the derivatives of benzene. Many derivatives of piperidine have been so prepared from the corresponding derivatives of pyridine.¹³¹

The pyrrole nucleus, unless it carries a carbethoxy group on the nitrogen, is extremely resistant to hydrogenation.^{124, 132a} In general, temperatures of 200° to 250° are required with a nickel catalyst. Pyrrole itself and the alkyl pyrroles are hydrogenated under these conditions to pyrrolidines in good yields. However, the pyrroles carrying a carbethoxy group in the 2-, 3-, 4-, or 5-position are likely to be so resistant to hydrogenation that the carbethoxy group is converted to a methyl group before the ring is hydrogenated. Pyrroles carrying a carbethoxy group on the nitrogen are more readily hydrogenated than many derivatives of benzene. For example, 1,3-dicarbethoxypyrrole has been converted rapidly to the corresponding pyrrolidine at a temperature of 70° over Raney nickel. *N*-Alkylpyrroles and their derivatives are slowly reduced with hydrogen and platinum at room temperature provided that oxygen is excluded and the catalyst is reduced separately.^{132b}

¹²⁷ Adkins and Reid, *J. Am. Chem. Soc.*, **63**, 711 (1941).

¹²⁸ Burger and Mosettig, *ibid.*, **57**, 2731 (1935), **58**, 1857 (1936).

¹²⁹ van de Kamp and Mosettig, *ibid.*, **57**, 1107 (1935).

¹³⁰ Adkins and Coomadt, *ibid.*, **63**, 1563 (1941).

¹³¹ Adkins, Kueck, Farlow, and Wojcik, *ibid.*, **56**, 2425 (1934).

¹³²(a) Rainey and Adkins, *ibid.*, **61**, 1104 (1939). (b) Sohl and Shriner, *ibid.*, **55** 3828 (1933).

HYDROGENOLYSIS

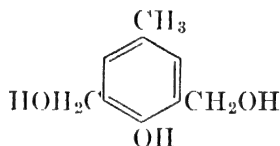
Hydrogenolysis of Alcohols

Reactions of the type $\text{ROH} + \text{H}_2 \rightarrow \text{RH} + \text{H}_2\text{O}$ take place readily only if R contains a phenyl, pyreryl, furyl, pyridyl, hydroxy, carbonyl, or carbalkoxy group. The reaction takes place readily when an alcohol, for

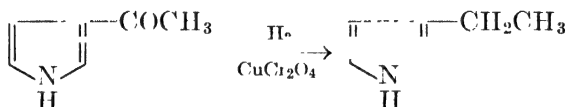
example, has the structure $\begin{array}{c} | \quad | \quad | \\ -\text{C}=\text{C}-\text{C}-\text{OH} \\ | \end{array}$ where the double bond is resistant to hydrogenation as in benzyl alcohol. This alcohol is converted almost quantitatively to toluene over nickel at 100° to 125° . Similarly, mandelic ester yields phenylacetic ester when hydrogenated at 175° over nickel.¹³³



o-Benzoylbenzoic ester is converted to *o*-benzylbenzoic ester over copper chromite at 200° . The alcoholic hydroxyls in substituted benzyl alcohols such as in



and di- and tri-aryl carbinols are readily replaced by hydrogens over copper chromite.¹³³ Acyl pyrroles such as



are converted to alkyl pyrroles¹²⁴ over either copper chromite or Raney nickel. The furan ring has a similar though less marked effect in labilizing hydroxyl groups toward hydrogenolysis, because the furan ring is more readily hydrogenated than a benzene or pyrrole ring, and thereby the labilizing effect of the unsaturated linkages is lost.¹³⁴ Methylfuran has been obtained from furfuryl alcohol over copper chromite at 200° . If the aromatic nucleus is more distant from the hydroxyl group as in phenylethyl alcohol the replacement of hydroxyl by hydrogen does not occur so readily as in the benzyl alcohols but nevertheless consti-

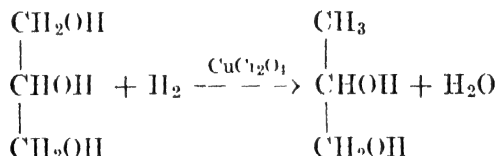
¹³³ Adkins, Wojcik, and Covert, *ibid.*, **55**, 1669 (1933).

¹³⁴ Burdick and Adkins, *ibid.*, **56**, 438 (1934).

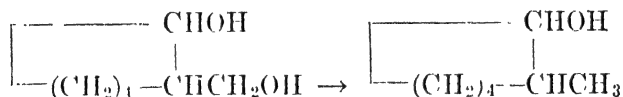
tutes an important side reaction when an attempt is made to hydrogenate the nucleus.

Copper chromite is in general more effective than nickel as a catalyst for hydrogenolysis of compounds of the types discussed just above. This is true because it is less active for the saturation of the unsaturated linkages upon which the labilization of the carbon-to-oxygen linkage depends.

Hydroxyl groups have a labilizing influence upon carbon-to-oxygen linkages, similar to that manifested by carbon-to-carbon double bonds. This effect is particularly evident in 1,3-glycols. Trimethylene glycol and 1,3-cyclohexanediol are converted rapidly at 200° over copper chromite to propyl alcohol and cyclohexanol, respectively. Glycerol also loses one hydroxyl group and 1,2-propanediol is formed.



If a glycol contains a secondary and primary hydroxyl, either one may be eliminated with the formation of isomeric alcohols. However, it would appear that the primary hydroxyl is the more readily eliminated since 1,3-butanediol gives almost twice as much 2-butanol as 1-butanol. Similarly, hydrogenation of the cyclic 1,3-glycol leads exclusively to the secondary alcohol.¹³⁵

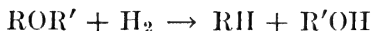


where n has a value of 3 or 4.

The 1,2- and 1,4-glycols are much more stable toward hydrogenolysis than the 1,3-glycols. In open-chain glycols the 1,2-compounds are more stable than the 1,4-glycols while with the cyclohexanediols the 1,4-glycol is the more stable.

The hydrogenolysis of carbon-to-oxygen linkages in some of the more highly substituted glycols has been noted in the later section on the hydrogenolysis of carbon-to-carbon linkages (p. 825).

¹³⁵ Connor and Adkins, *ibid.*, **54**, 4678 (1932).

Hydrogenolysis of Ethers ¹³⁶

Aryl alkyl ethers are in general quite stable toward hydrogenolysis and even over Raney nickel undergo hydrogenation rather than hydrogenolysis. Dialkyl ethers are quite stable toward hydrogen over nickel at temperatures below about 250°, at which temperature carbon-to-carbon cleavage may occur.

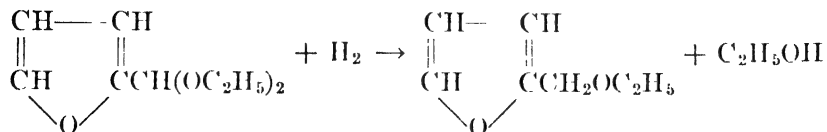
The benzyl ethers are very readily cleaved over Raney nickel at temperatures of 100° to 150°, toluene and an alcohol or phenol being formed invariably. The benzyl aryl ethers are cleaved at a somewhat lower temperature than the benzyl alkyl ethers. The diaryl ethers require a somewhat higher temperature for hydrogenolysis, i.e., 150° to 200°. Over Raney nickel there is very little hydrogenation of these ethers, but over nickel on kieselguhr a number of ethers react by hydrogenation rather than by hydrogenolysis. The readiness of the cleavage of benzyl ethers is another illustration of the effect of a double bond in the 2-position in labilizing the carbon-to-oxygen bond.

The ether linkage in tetrahydrofuran derivatives is quite stable toward hydrogenolysis, but because of the influence of the double bonds the furan derivatives are cleaved by hydrogen at 175° or lower.

Nickel is probably a more active catalyst than copper chromite for the hydrogenolysis of ethers. Copper chromite is a better catalyst for the cleavage of furanoid compounds, since it is less active toward double bonds; hence those important labilizing groups are not hydrogenated until after hydrogenolysis has occurred. Copper chromite was also used by Zartman ⁵⁶ for the hydrogenolysis of the ether 1,1-diphenyl-2-phenoxyethylene at 200°.

Hydrogenolysis of Acetals ^{37, 134}

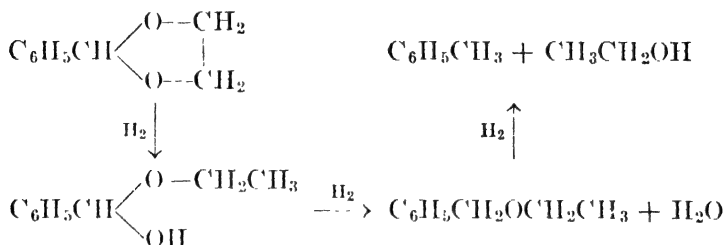
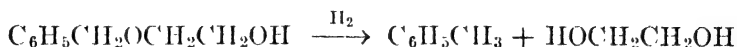
The same conditions that are favorable to the hydrogenolysis of ethers also result in the hydrogenolysis of acetals. Diethyl furfural acetal is converted in 97 per cent yield over nickel (*k*) or Raney nickel at 175° to furfuryl ethyl ether.



¹³⁶ Van Duzee and Adkins, *ibid.*, **57**, 147 (1935).

If a little of any one of several amines is added to the reaction mixture, then the reaction is primarily one of hydrogenation and the diethyl acetal of tetrahydrofurfural is produced in a 76 per cent yield.

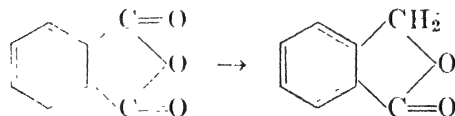
The course of the hydrogenation of a cyclic acetal (benzylidene acetal of ethylene glycol) may be represented thus:



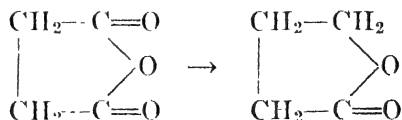
The above scheme accounts for the products obtained at 125°, i.e., toluene, ethanol, ethylene glycol, benzyl ethyl ether, and the mono-benzyl ether of ethylene glycol. At 175° these same products were obtained, accompanied by the corresponding hexahydro compounds. Ethylene glycol and hydrocarbons were obtained at 175° from the benzyl ether of ethylene glycol. The hydrogenation of the benzylidene ether of trimethylene glycol and of the 1,2-benzylidene ether of glycerol yielded results similar to those obtained from the ether of ethylene glycol except that the hydrogenation proceeded more slowly.

Hydrogenolysis of Acid Anhydrides and Imides

Both phthalic and succinic anhydrides were reduced with hydrogen to give lactones as well as more completely hydrogenated products. Phthalic anhydride over nickel at 150° or copper chromite at 260° was converted to phthalide¹³⁷ in 80 per cent yields,

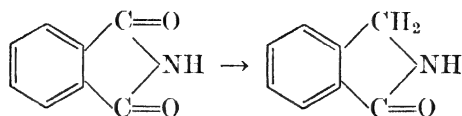


while succinic anhydride over copper chromite at 250° gave a 29 per cent yield of butyrolactone:

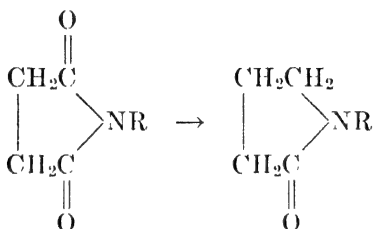


¹³⁷ Austin, Bousquet, and Lazier, *ibid.*, **59**, 864 (1937).

A similar transformation is the hydrogenolysis of phthalimide to phthalimidine ⁹⁷ in an 80 per cent yield at 200° over nickel (*k*):



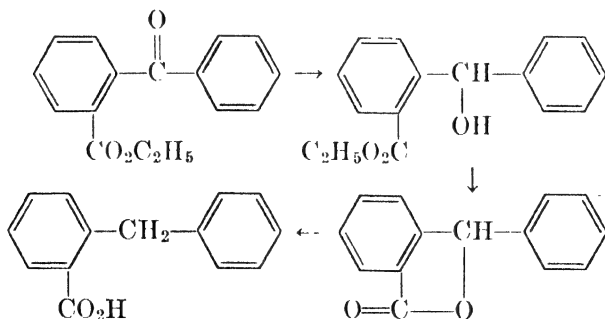
N-substituted succinimides and glutarimides have also been converted to the corresponding pyrrolidones or piperidones ¹³⁸ over Raney nickel at 220° in dioxane solution where R is $-\text{CH}_2\text{CH}_2\text{C}_6\text{H}_{11}$ or $-\text{C}_5\text{H}_{11}$.



Hydrogenolysis of Esters and Lactones ¹³⁹



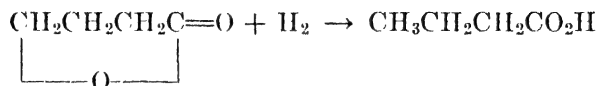
Certain esters and lactones readily undergo hydrogenolysis; benzyl acetate, for example, was quantitatively converted to toluene and acetic acid at 135° over nickel. The reaction is not complete unless an amine (N,N-dimethylcyclohexylamine) is used as a solvent to neutralize the acid as it is produced. *o*-Benzoylbenzoic ester is converted in 95 per cent yield over nickel (*k*) at 150° to *o*-benzylbenzoic acid. The reaction probably involves, first, the hydrogenation of the carbonyl; second, the formation of a lactone; and then the hydrogenolysis of the lactone:



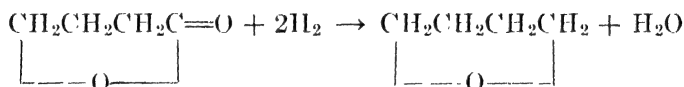
¹³⁸ Paden and Adkins, *ibid.*, **58**, 2487 (1936).

¹³⁹ Wojcik and Adkins, *ibid.*, **55**, 4939 (1933).

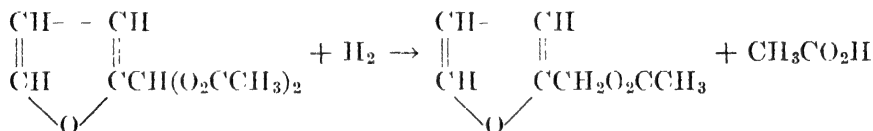
Certain lactones have been converted in 70 to 80 per cent yields to the glycols, yet the hydrogenolysis to the acid is always a possible source of difficulty with such compounds, i.e.,



The oxygen of the carbonyl group may also undergo cleavage with the formation of tetrahydrofurans.



Furfural diacetate¹³⁴ readily undergoes hydrogenolysis with the formation of considerable amounts of furfuryl acetate:

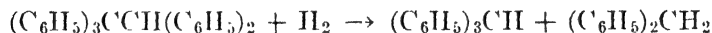


Hydrogenation also occurs, so that other products are produced.

Hydrogenolysis of Carbon-Carbon Linkages

Carbon-to-carbon linkages are in some cases cleaved by hydrogen under the conditions used for hydrogenation with nickel and copper chromite catalysts.⁵⁶ Alkyl and aryl groups as well as oxygen and nitrogen as substituents labilize a carbon-to-carbon linkage toward hydrogenolysis.

Pentaphenylethane is cleaved by hydrogen at 125° over nickel and at 200° over copper chromite.



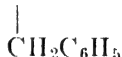
Tetraphenylethane is also cleaved under somewhat more drastic conditions, but triphenylethane is stable toward hydrogen over nickel and copper chromite at least up to 250°. The unsaturated phenyl group is much more effective in labilizing carbon-to-carbon bonds than are the saturated groups. Even the highly substituted pentacyclohexylethane is resistant to hydrogenolysis.

A single oxygen does labilize a carbon-to-carbon linkage, for an alcohol of the type RCH_2OH reacts with hydrogen over Raney nickel with a rupture of the linkage between R and the carbinol carbon, but the temperature required for this reaction is rather high (250°) and even

then the reaction proceeds slowly.¹⁴⁰ However, two oxygens in the 1,3-positions with respect to each other exert a powerful influence in facilitating hydrogenolysis. The diketone, $(\text{CH}_3)_3\text{C}_6\text{H}_2\text{C}'\text{OCH}_2\text{COC}'\text{H}_3$, gives a 25 per cent yield of $(\text{CH}_3)_3\text{C}_6\text{H}_2\text{COCH}_3$ at 125° over Raney nickel. A more highly substituted 1,3-diketone, $\text{C}_6\text{H}_5\text{C}'\text{OCHCOC}'\text{H}_3$,

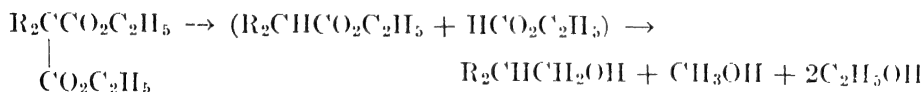
$\begin{array}{c} | \\ \text{CH}_2\text{C}_6\text{H}_5 \end{array}$

undergoes hydrogenolysis at carbon linkages to the extent of more than 68 per cent at 60° , while $\text{CH}_3\text{C}'\text{OCHCOC}'\text{H}_3$ gives a 40 per cent yield of



$\text{CH}_3\text{C}'\text{OCH}_2\text{CH}_2\text{C}_6\text{H}_5$.

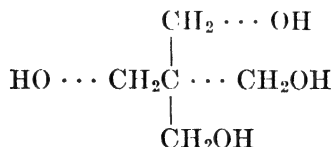
The combination of alkyl and oxygen substitution is the most effective structure for labilization toward hydrogenolysis. As noted elsewhere in this chapter, disubstituted malonic esters undergo hydrogenolysis quantitatively in the sense of the reaction



Substituted β -keto esters show a similar type of reaction. For example, in an acetoacetic ester $\text{CH}_3\text{C}'\text{O} \cdots \text{CHRC}'\text{O}_2\text{C}_2\text{H}_5$, where R was *n*-butyl, cleavage occurred at the dotted linkage to the extent of 71 per cent, while when R was benzyl the cleavage was quantitative. Ethyl dimethylacetoacetic ester underwent the following reaction:



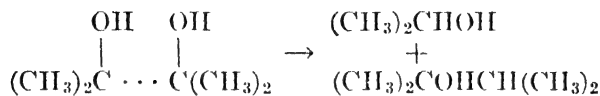
Branched-chain alkyl groups are even more effective than straight-chain substituents in facilitating the cleavage of β -diketones,¹⁴¹ and a β -keto, β -hydroxy, or malonic ester. For example, $\text{Me}_3\text{CC}'\text{OCH}_2\text{COC}'\text{H}_3$ is cleaved to a greater extent than $\text{CH}_3\text{C}'\text{OCH}_2\text{COC}'\text{H}_3$. The 1,3-glycols behave similarly to these ketones and esters. For instance, 2-methyl-2,4-pentanediol $(\text{CH}_3)_2\text{C}'(\text{OH}) \cdots \text{CH}_2\text{CHOHC}'\text{H}_3$ is cleaved within thirty minutes to give an 86 per cent yield of isopropyl alcohol. (The linkages undergoing hydrogenolysis are indicated by dotted lines in the formulas.)



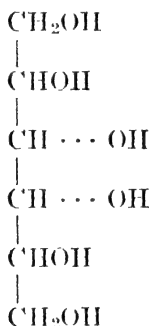
¹⁴⁰ Wojcik and Adkins, *ibid.*, **55**, 1293 (1933).

¹⁴¹ Sprague and Adkins, *ibid.*, **56**, 2669 (1934).

Pentaerythritol cleaved quantitatively at one carbon-to-carbon and at two carbon-to-oxygen linkages to give isobutyl and methyl alcohols. Even pinacol, a 1,2-glycol, suffered carbon-to-carbon cleavage to the extent of 17 per cent, along with a similar amount of carbon-to-oxygen cleavage to give dimethylisopropylcarbinol:



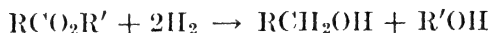
A sufficient accumulation of hydroxyl groups even without alkyl substitution makes hydrogenolysis of carbon-to-carbon linkages possible. Sorbitol or mannitol¹⁴² at 250° over copper chromite gave a high yield of 1,2-propylene glycol along with smaller yields of methanol and ethanol. Propylene glycol is also the major product in a rather complete hydrogenolysis of glucose, lactose, maltose, and sucrose. Less complete reaction of hydrogen with the sugars and alcohols gave larger yields of products not involving the breaking of carbon-to-carbon bonds. The probable weak bonds in sorbitol are indicated by dots in the formula.



The relative effectiveness of groups in labilizing the hydrogenolysis of carbon-to-carbon linkages cannot be stated quantitatively. However, a study of the data available from several investigations indicates that among the common radicals the order of increasing effectiveness is methyl, ethyl, benzyl, isopropyl, *t*-butyl, phenyl, mesityl, hydroxyl, carbonyl, carbinyl, and acyl.

Hydrogenolysis of Esters to Alcohols^{133, 143, 144}

Many esters are reduced to alcohols by hydrogen over copper chromite at 200° to 300° under 100 to 300 atmospheres of hydrogen.

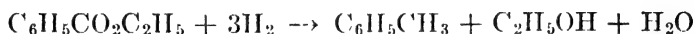


¹⁴² Zartman and Adkins, *ibid.*, **55**, 4559 (1933).

¹⁴³ Adkins and Folkers, *ibid.*, **53**, 1095 (1931).

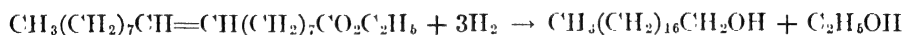
¹⁴⁴ Wilbur Lazier, U. S. pat., 2,079,414, and others.

The reaction goes smoothly and almost quantitatively where R is a saturated, straight or branched or cyclic chain. The method is not applicable to esters where R carries a halogen or sulfur atom since these will react with hydrogen or deactivate the catalyst. If R is a phenyl or pyrrole nucleus the hydrogenation will proceed beyond the alcohol stage. For example, ethyl benzoate gives toluene.

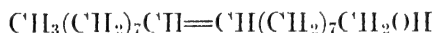


However, if the aromatic nucleus is two carbon atoms distant from the carbalkoxy group it is without effect upon the hydrogenation. For example, ethyl β -phenylpropionate is smoothly converted to 3-phenylpropanol-1. Ethyl α -phenylacetate gives both types of reaction, i.e., phenylethyl alcohol and ethylbenzene.

If R contains an alkene linkage or aldehyde or ketone group these groups will be saturated by hydrogen before the conditions necessary for the hydrogenation of a carbalkoxy group are reached. For example, ethyl oleate upon hydrogenation over copper chromite gives octadecyl alcohol.



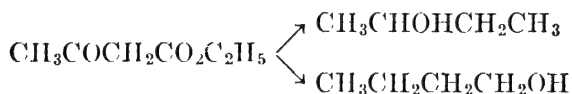
If zinc chromite is used as a catalyst at 300° to 325° reaction occurs preferentially at the carbalkoxy group, but the oleyl alcohol,



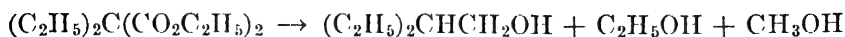
so prepared is contaminated with octadecyl alcohol.

A pyridinoid ring in R will also be hydrogenated before the carbalkoxy group is converted to a carbinol, so that the product will be an alcohol derived from piperidine rather than from pyridine. The piperidine obtained will usually be alkylated on the nitrogen atom, under these conditions.

If nitrogen or oxygen atoms are in the β -position with respect to the carbalkoxy group, cleavage (hydrogenolysis) may occur. For example, acetoacetic ester gives a mixture of 1- and 2- butanol:



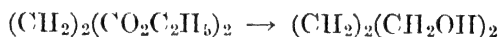
Malonic ester gives propanol-1 rather than trimethylene glycol. If the carbon atom between the carbons carrying oxygen is substituted, as in the ethyl ester of diethylmalonic acid, then hydrogenolysis of a carbethoxyl group takes place. There are formed in this instance 2-ethylbutanol-1 and ethyl and methyl alcohol.



A nitrogen atom is similar to oxygen in labilizing a carbon-to-oxygen bond for cleavage. For example, β -piperidinopropionic ester goes to *N*-*n*-propylpiperidine:

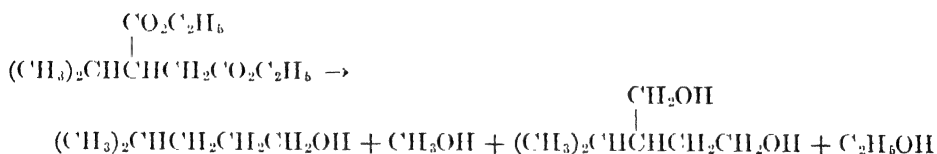


Oxygen or nitrogen in either the α - or γ -position with respect to a carbalkoxy group is less effective in labilizing cleavage than if they were in the β -position, for α - and γ -hydroxy esters may be converted to the corresponding glycols in good yields. Though it is impossible to prepare a glycol from a malonic ester by catalytic hydrogenation, the succinic esters go well into 1,4-glycols.



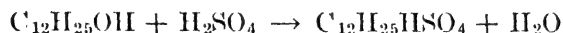
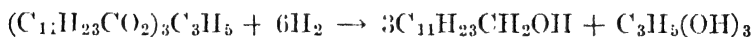
If the hydrogenation is not carried out rather rapidly with a good catalyst and a sufficiently high pressure of hydrogen, products other than glycol may be produced in considerable amounts, i.e., ethyl β -hydroxy butyrate, butyrolactone, butyric acid, and tetrahydrofuran.

A substituted succinic ester, diethyl α -methylsuccinate, gave a 72 per cent yield of the glycol, but the ester having an isopropyl group in the α -position gave over twice as much isohexyl alcohol as of the glycol corresponding to the succinate.



The tendency toward hydrogenolysis of a carbon-to-carbon chain with increase in branching of the chain is quite general, as noted elsewhere.

The most important commercial application of the hydrogenation of esters to alcohols is the conversion of cocoanut oil and other glycerides to alcohols, useful in the manufacture of detergents. The steps in the process using glyceryl laurate as the ester, are as follows:



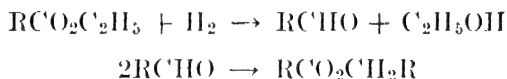
The glycerol undergoes hydrogenolysis to propylene glycol and propyl alcohol.

The hydrogenation of esters to alcohols in most instances goes smoothly and almost quantitatively. However, side reactions may

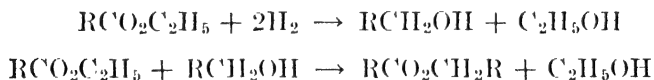
occur if the ester is impure, if the catalyst is improperly prepared, or if the pressure of hydrogen is too low. The copper in the catalyst may be reduced from the bivalent to the univalent state if water or acids are present in the mixture being hydrogenated. The deactivation of the catalyst under these circumstances is shown by a change in color from the black copper chromite to a reddish cuprous compound.

The hydrogenation of esters is apparently a reversible process in the sense that the alcohols and glycols produced react to form esters. The concentration of the esters so produced is of the order of a few per cent at 250–260° under 100 atmospheres of hydrogen. At higher pressures, 250–300 atmospheres, the concentration of esters at equilibrium is no more than 1 per cent. However, if the catalyst is deactivated before the completion of the reaction, very considerable amounts of ester may be present.

These esters may result from the reaction of two moles of an aldehyde resulting from the partial hydrogenation of the ester.



As a matter of fact, esters so related to the starting ester are often found in the reaction mixture. Such an ester might result from alcoholysis according to the reactions



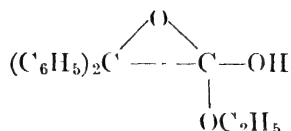
But the amounts sometimes found point to the validity of the mechanism involving the aldehyde. An active catalyst will, of course, catalyze the hydrogenation of the ester $\text{RCO}_2\text{CH}_2\text{R}$ to two moles of RCH_2OH .

Levene¹⁴⁵ found that certain hydroxy esters and amino esters could be hydrogenated over copper chromite at a relatively low temperature (175°). Equal amounts of catalyst and of the ester in methanol were used. These reductions depend upon large ratios of catalyst which make possible the use of a lower temperature at which hydrogenolysis of the desired reduction product does not take place to any considerable extent. Levene and his associates¹⁴⁶ were also successful in reducing the ethyl esters of leucine and phenylamino acetic acid to the corresponding amino alcohols with Raney nickel at 40° to 70° in 9 to 18 hours. The yields were 40 per cent of $(\text{CH}_3)_2\text{CHCH}_2\text{CHNH}_2\text{CH}_2\text{OH}$ and 60 per cent of $\text{C}_6\text{H}_5\text{CHNH}_2\text{CH}_2\text{OH}$.

¹⁴⁵ Levene, Meyer, and Kuna, *J. Biol. Chem.*, **125**, 703 (1938).

¹⁴⁶ Ovakinian, Kuna, and Levene, *J. Am. Chem. Soc.*, **62**, 676 (1940).

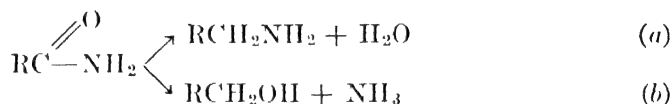
The lowest temperature at which the hydrogenation of an ester has been reported over copper chromite is 125° for ethyl benzilate, $(C_6H_5)_2COHCO_2C_2H_5$. It seems probable that this ester exists in a tautomeric form



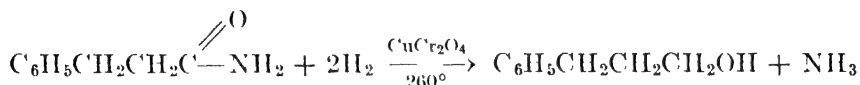
Since this is the hemiacetal of an oxido ketone, its easy hydrogenation is understandable.

Hydrogenolysis of Amides to Amines ¹⁴⁷

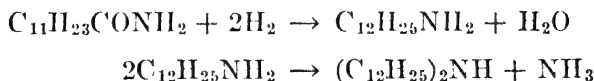
The reduction of an amide may lead to an amine or an alcohol, depending upon whether cleavage occurs at the oxygen or at the nitrogen-to-carbon linkage.



Reduction of an amide with sodium and an alcohol gives alcohols; catalytic hydrogenation over copper chromite gives the amine in most instances. It is possible that even in catalytic hydrogenation the alcohol is first formed and then reacts with the ammonia to give an amine and water. There are no experiments which show conclusively the course of the reaction in catalytic hydrogenation, although unquestionably the alcohol is sometimes the major product. For instance, the amide of β -phenylpropionamide was converted in high yield to 3-phenylpropanol-1.



The yields of primary amines by the hydrogenation of unsubstituted amides are seldom above 50 per cent, because the temperature of hydrogenation is so high (250–260°) that the first-formed primary amine reacts with itself to form a secondary amine. For example, lauramide gave almost equal yields of dodecyl- and didodecylamine.



The hydrogenation of monosubstituted amides usually takes place smoothly. For example, N-cyclohexyllauramide and N-phenethyl-

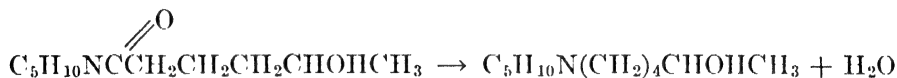
¹⁴⁷ Wojcik and Adkins, *ibid.*, **56**, 2419 (1934).

heptamide gave the corresponding cyclohexyldodecylamine and heptyl phenethylamines in yields of the order of 60 per cent after hydrogenation for less than twenty minutes at 250°.

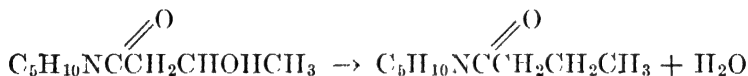
N-Acylpiperidines are converted in good yields to the corresponding alkylpiperidines.



The N-acylpiperidines carrying a hydroxyl group in the α -, β -, γ -, or δ -position in the acyl group have been converted in 50 to 80 per cent yields to the corresponding amino alcohols.

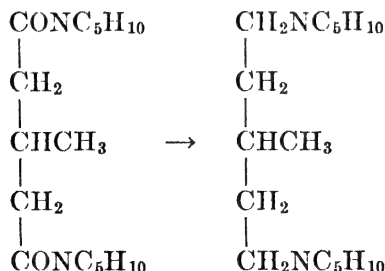


Raney nickel catalyzed the same reaction, but the yields of amino alcohols were not so good. However, nickel is useful for converting a β -hydroxyamide to an amide.

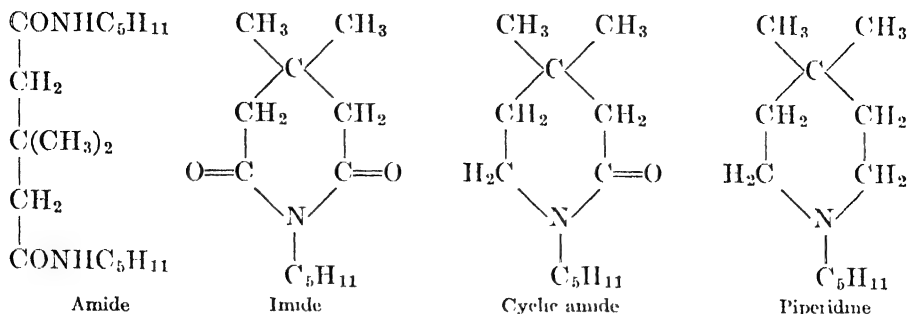


Copper chromite catalyzes the same transformation, but the amido group is also hydrogenated so that the product is $\text{C}_5\text{H}_{10}\text{N}(\text{CH}_2)_3\text{CH}_3$. More highly substituted amides, such as the amide derived from mucic acid and piperidine, give many different products as the result of hydrogenation and hydrogenolysis.

The di-N-pentamethylene amide of β -methylglutaric acid was readily hydrogenated in 70 per cent yield to the diamine.

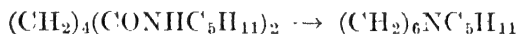


However, the monosubstituted amides of glutaric acid yield N-substituted piperidines, the imide and a cyclic amide probably being intermediate steps.¹³⁸



The yields of the piperidine from the amide, imide, or cyclic amide are good over copper chromite. Raney nickel proved to be a useful catalyst for converting the imide to the cyclic amide.

Amides of succinic acid may be converted to pyrrolidines by hydrogenation over copper chromite while succinimides over Raney nickel may be hydrogenated to cyclic amides. Amides of adipic acid may be converted to hexahydroazepines.



Hydrogenolysis of Organometallic Compounds

Gilman, Jacoby, and Ludeman¹⁴⁸ showed that the phenyl derivatives of calcium, lithium, sodium, potassium, rubidium, and cesium underwent hydrogenolysis without an added catalyst. The reaction was of the type $\text{C}_6\text{H}_5\text{K} + \text{H}_2 \rightarrow \text{C}_6\text{H}_6 + \text{KH}$ and took place at room temperature within 10 to 110 minutes under a pressure of 1 to 2 atmospheres of hydrogen. Several alkyl and aryl lithium compounds underwent hydrogenolysis under these same conditions. Earlier work had shown that the triphenyl derivatives of phosphorus, arsenic, antimony, and bismuth were cleaved by hydrogen at 60 atmospheres at 225° to 350°.¹⁴⁹ Compounds of the type $(\text{C}_6\text{H}_5)_3\text{Sb}$, $(\text{C}_6\text{H}_5)_4\text{Pb}$, $(\text{C}_4\text{H}_9)_2\text{Zn}$, and $(\text{C}_6\text{H}_5)_2\text{Mg}$ underwent hydrogenolysis over a nickel catalyst at 160° to 200° under 125 atmospheres of hydrogen.¹⁵⁰

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¹⁴⁸ Gilman, Jacoby, and Ludeman, *ibid.*, **60**, 2336 (1938).

¹⁴⁹ Ipatieff, Razuwajeff, and Bogdanow, *Ber.*, **63**, 335, 1110 (1930).

¹⁵⁰ Zintman and Adkins, *J. Am. Chem. Soc.*, **54**, 3398 (1932).

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CHAPTER 10

ORGANIC SULFUR COMPOUNDS *

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I. INTRODUCTION

This chapter will be limited to the consideration of organic compounds in which the most prominent chemical properties are due to a functional group containing sulfur. Probably the most important sulfur compounds excluded by this limitation are heterocycles, in which the chemical behavior is modified by the influence of sulfur upon the rest of the molecule but usually is not chiefly dependent upon the presence of sulfur.

The names of the types of sulfur compounds to be considered and the structures of their parent substances are listed in Table I. Some of these structures are not universally accepted or represent compounds which are hypothetical but of which derivatives are known. These will be discussed in the sections devoted to the appropriate series.

TABLE I
COMPOUNDS WITH FUNCTIONAL GROUPS CONTAINING SULFUR

| <i>Names</i> | <i>Formulas *</i> | <i>Names</i> | <i>Formulas *</i> |
|---|---|-----------------------|---|
| Sulphydryl compounds (mercaptans and thiophenols) | $R-S-H$ | | $\begin{array}{c} O \\ \uparrow \\ R-S-SH \\ \downarrow \\ O \end{array}$ |
| Sulfides | $R-S-R$ | Thiolsulfonic acids † | |
| Disulfides | $R-S-S-R$ | | $\begin{array}{c} O \\ \uparrow \\ R-S-OH \\ \downarrow \\ O \end{array}$ |
| Polysulfides † | $R(S)_nR$ ($n = 3, 4, 5$) | Sulfinic acids † | $R-S-OH$ |
| | | Sulfenic acids † | $R-S-OH$ |
| Sulfonium salts | $\left[\begin{array}{c} R \\ \\ R-S-R \end{array} \right]^+ X^-$ | | $\begin{array}{c} S \\ \\ R-C-H \end{array}$ |
| | $\begin{array}{c} O \\ \uparrow \\ R-S-R \end{array}$ | Thioaldehydes | |
| Sulfoxides | | | $\begin{array}{c} S \\ \\ R-C-R \end{array}$ |
| | $\begin{array}{c} O \\ \uparrow \\ R-S-R \\ \downarrow \\ O \end{array}$ | Thioketones | |
| Sulfones | | Thio acids | $\begin{array}{c} O \\ \\ R-C-SH \end{array}$ |
| | $\begin{array}{c} O \\ \uparrow \\ R-S-OH \\ \downarrow \\ O \end{array}$ | Thiol acids † | |
| Sulfonic acids | | | $\begin{array}{c} S \\ \\ R-C-OH \end{array}$ |
| | | Thion acids † | |
| | | | $\begin{array}{c} S \\ \\ R-C-SH \end{array}$ |

* The usual conventions (p. 1829) are followed in designating normal and coordinate covalent links.

† The structures of these compounds are considered in more detail in the discussion of the appropriate series.

Since oxygen and sulfur are in the same group of the periodic table, similarities in the behavior of their organic derivatives might be expected. The differences between sulfur and oxygen compounds can usually be attributed to one of the following: (1) The sulfur kernel has one more electron layer than the oxygen kernel. Therefore, the former has the smaller effective nuclear charge (smaller inductive effect) and the greater electron mobility (p. 1842). (2) In some cases the fact that the sulfur compounds have higher molecular weights than their oxygen analogs is the chief factor responsible for differences in physical properties. (3) Whereas oxygen is unable to expand its valence shell (p. 1837) there are some indications (pp. 1839, 879-882) that sulfur may do so; therefore oxygen and sulfur analogs may react by different mechanisms.

In considering the functional reactions of sulfur compounds it is usually true that the reactions of one series are methods of preparation for other series. It has not seemed logical to discuss subjects consistently in the latest possible location, since this would frequently emphasize reactions from their less important aspect. The arrangement of the material is therefore arbitrary, but sufficient cross references will make the discussion of each series complete in itself.

The differences in the reactions of the alkyl and aryl derivatives are less in the sulfur than in the oxygen series. In general, therefore, it will not be necessary to discuss separately compounds in which sulfur is attached to aromatic and aliphatic groups. However, in reactions of a given sulfur function with aliphatic and aromatic compounds, the usual differences in reactivity are observed and may require separate consideration; for example, the methods for the introduction of the —SR group into an aliphatic chain will be different from those for its introduction into an aromatic nucleus. In the equations accompanying the discussion the symbol R will be used to include both aliphatic and aromatic radicals unless otherwise noted. When reactions are limited to aromatic compounds the radicals will be abbreviated as Ar.

In discussing the various series of sulfur compounds the presentation will be generalized. Specific compounds will be mentioned only when it is necessary for the sake of illustration, when the compounds are especially important, or when the reactions outlined may not be general. Polyfunctional compounds will be mentioned only when they differ markedly from what might be expected from a knowledge of the monofunctional types. Although some attention will be given to structure and physical properties, the chief emphasis will be upon methods of preparation and reactions of the various series.

II. SULFHYDRYL COMPOUNDS¹

General Characteristics

Occurrence. Mercaptans are present in petroleum distillates. Although they constitute a small percentage of the distillate, the large amount of petroleum refined makes the mercaptans the most readily available of the organic sulfur compounds. The amount of mercaptans which could be obtained from this source is of the order of hundreds of tons daily¹ in the United States alone. Unfortunately, there are no uses so extensive as to require mercaptans in this quantity; as a result those not removed by extraction with alkali are converted to disulfides, which are allowed to remain in the petroleum product. However, large amounts of a mercaptan mixture, containing mostly ethyl mercaptan with considerable amounts of methyl mercaptan and higher mercaptans, are available from the refining of gasoline.

Methyl mercaptan is a product of the anaerobic bacterial decomposition of gelatin and albumin. It is partly responsible for the odor of feces² and is present in urine³ after asparagus has been eaten. Butyl mercaptan is present in the defensive secretion of the skunk.⁴

Odor. The offensive odor of the low-molecular-weight mercaptans is probably the most notorious characteristic of organic sulfur compounds. It has been estimated⁵ that 0.000,000,002 mg. (one part in fifty billion) of ethyl mercaptan in air may be detected by odor. The unpleasantness and intensity of the mercaptan odors decrease with an increase in the carbon chain; *n*-decyl and lauryl mercaptans have no more odor than the corresponding alcohols. The odors of thiophenols of low molecular weight are also unpleasant, but the higher members of the series are less disagreeable.

Toxicity. Care should be used in handling mercaptans and thiophenols. Direct contact with thiophenols may produce an irritation⁶ of the skin similar to that of ivy poisoning. Mercaptans produce various symptoms⁷ such as drooping of the lids, increased sensitivity of the eyes to light, giddiness, headache, or severe irritations of the skin.

¹ Mahloff, Marks, and Hess, *Chem. Rev.*, **7**, 493 (1930). This paper, "A Study of Mercaptan Chemistry," covers more than 50 pages and includes more than 600 references.

² Nencki and Sieber, *Monatsh.*, **10**, 526 (1889); Nencki, *ibid.*, **10**, 862 (1889); *Ber.*, **34**, 201 (1901).

³ Nencki, *Ber.*, **25**, 512c (1892).

⁴ Beckmann, *Pharm. Zentralhalle*, **37**, 557 (1896).

⁵ Fischer and Penzoldt, *Ann.*, **239**, 131 (1887).

⁶ Hofmann and Baumann, *Ber.*, **20**, 2251 (1887); Jacobsen, *Ann.*, **277**, 220 (1893). Huebner and Mueller, *Z. Chem.*, [2] **7**, 14 (1871); Hunter, *J. Chem. Soc.*, **127**, 911 (1925).

⁷ Weber, *Ber.*, **33**, 795 (1900); Grandjean-Hirter, *Chem. Zentr.*, **11**, 1181 (1916).

Solubility. Sulfhydryl compounds are usually less soluble in water than the corresponding hydroxyl compounds. Ethyl mercaptan, for example, is soluble to the extent of 1.5 g. in 100 cc. of water. Both mercaptans and thiophenols exhibit normal solubility in organic solvents.

Boiling Points. The high-molecular-weight mercaptans have higher boiling points (Fig. 1) than the corresponding alcohols. However, in

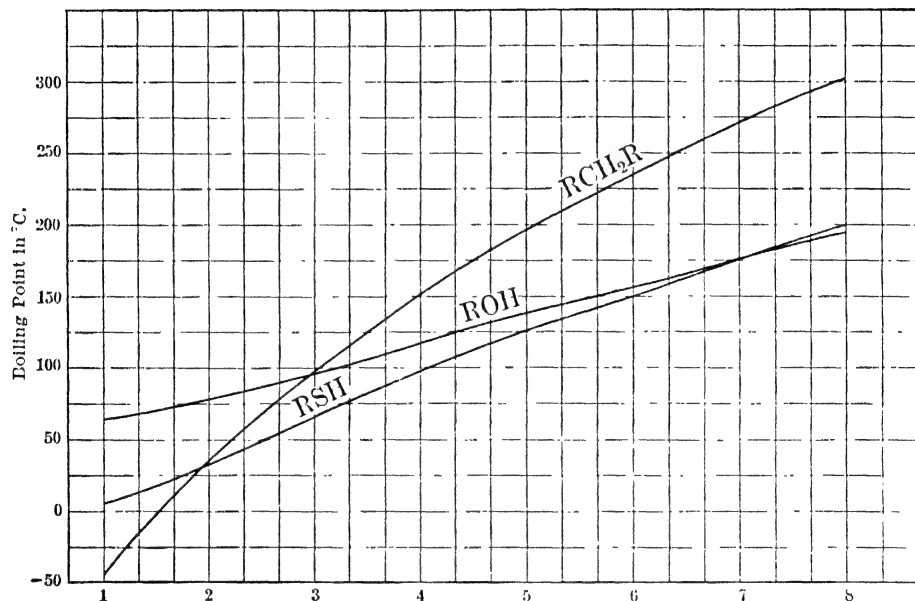


FIG. 1.—Number of carbon atoms in R ($R = C_nH_{2n+1}$). Comparison of the boiling points of alcohols, mercaptans, and hydrocarbons.

the lower members of the series the greater association of the alcohols causes them to have the higher boiling points, as might be expected by a comparison of the boiling points of hydrogen sulfide (b.p. -61.8°) and water. In the case of the *n*-heptyl derivatives, association of the alcohol is enough to compensate for the higher atomic weight of sulfur in the mercaptan; the two analogs, therefore, have the same boiling point. Similarly, thiophenol has a lower boiling point than phenol, the thiocresols have about the same boiling points as the cresols, and higher thiophenols boil higher than the corresponding phenols. Verification of the opinion that the sulfhydryl group has less tendency than the hydroxyl group to undergo association is found (a) in spectroscopic data⁸ which show that *p*-thiocresol is not polymerized in the solid state and (b) in studies⁹ of heats of mixing which show that the weak donor

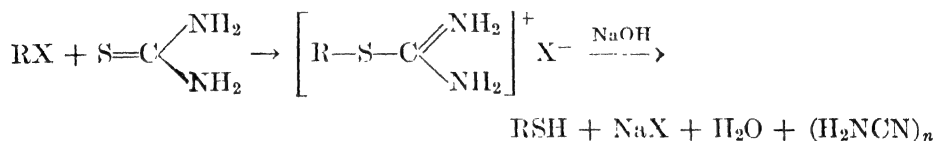
⁸ Gordy and Stanford, *J. Am. Chem. Soc.*, **62**, 498 (1940).

⁹ Copley, Marvel, and Ginsberg, *ibid.*, **61**, 3161 (1939).

ability of sulfur is responsible for the failure of thiophenol to be associated. The latter studies also indicate that hydrogen of the sulfhydryl group may form bonds with donor oxygen or nitrogen in the case of thiophenol but not in the case of *n*-heptyl mercaptan.

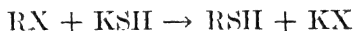
Preparation of Mercaptans

Hydrolysis of S-Alkylisothiuronium Salts. Alkyl halides^{10, 11} and alkyl sulfates¹² react readily with thiourea, giving isothiuronium salts. Addition of alkali liberates the free isothiourcas, but these are not stable and decompose to give mercaptans (80–90 per cent) and polymers of cyanamide. Dihalides may be converted¹⁰ to dithioglycols by this method.



Alkyl chlorides react rather slowly^{11, 13} and require a longer reflux period than the bromides and iodides. Isothiuronium salts may also be prepared directly¹³ from an alcohol (using dry hydrogen chloride) and thiourea. Isothiuronium salts make satisfactory derivatives¹¹ for the identification of alkyl bromides and chlorides. S-Benzylisothiuronium salts of organic acids are useful¹⁵ as derivatives for the identification of the acids.

Action of Alkylating Agents on Metal Hydrosulfides. Mercaptans are prepared¹⁶ also by the reaction of alkyl halides with an alcoholic solution of sodium or potassium hydrosulfide.



Other alkylating agents behave similarly; sodium ethyl sulfate was the alkylating agent in the first¹⁷ mercaptan synthesis. The hydrosulfide solution may be prepared by saturating alcoholic alkali with hydrogen sulfide; in this case potassium hydroxide is generally used because po-

¹⁰ (a) Renshaw and Searle, *J. Am. Chem. Soc.*, **59**, 2057 (1937); (b) Olin and Dains, *ibid.*, **52**, 3322 (1930); (c) v. Braun, *Ber.*, **42**, 4568 (1909).

¹¹ Urquhart, Gates, and Connor, *Org. Syntheses*, **21**, 36 (1941).

¹² Arndt, Milde, and Eckert, *Ber.*, **54**, 2236 (1921).

¹³ Johnson and Sprague, *J. Am. Chem. Soc.*, **58**, 1348 (1936).

¹⁴ Brown and Campbell, *J. Chem. Soc.*, 1699 (1937).

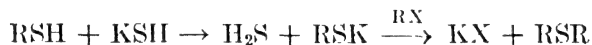
¹⁵ Donleavy, *J. Am. Chem. Soc.*, **58**, 1004 (1936).

¹⁶ (a) Fore and Bost, *ibid.*, **59**, 2557 (1937); (b) Ellis and Reid, *ibid.*, **54**, 1686 (1932)
(c) Hofmann and Cahours, *J. Chem. Soc.*, **10**, 320 (1858).

¹⁷ Zeise, *Ann.*, **11**, 1 (1834); Liebig, *Ann.*, **11**, 14 (1834).

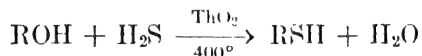
tassium sulfide is more soluble than sodium sulfide in alcohol. Under some conditions (for example, when a secondary halide is used) the complete absence of water is desirable, and better results are obtained by treating absolute alcoholic solutions of the alkoxides with hydrogen sulfide.

Since the mercaptans react with alkali to give mercaptides which may react with alkylating agents (p. 854), alkyl sulfides are by-products in the preparation of mercaptans by this method.



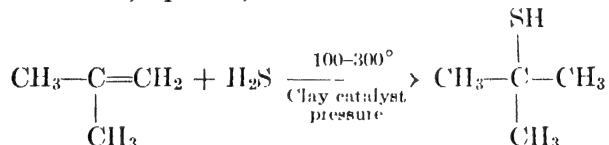
This side reaction may be minimized by maintaining an excess of hydrogen sulfide, either by carrying out the reaction under pressure or by passing in hydrogen sulfide during the reaction.

Catalytic Alkylation of Hydrogen Sulfide. Passage of an alcohol and hydrogen sulfide over thoria at elevated temperatures produces the mercaptan.



The reaction is not complete; about 50 per cent of *n*-butyl mercaptan is produced¹⁸ by one passage of *n*-butyl alcohol and hydrogen sulfide over the catalyst. This method was used in a small plant for the production of *n*-butyl mercaptan, which was under consideration as a camouflage gas (1917-1918).

Addition of Hydrogen Sulfide to Olefins. The addition of hydrogen sulfide to olefins does not occur readily and requires high pressures and temperatures. The products are those expected from Markownikoff's rule ("normal addition," p. 638).



It appears¹⁹ that unsaturated terpenes react with hydrogen sulfide more readily than do simple olefins.

Various catalysts for this reaction have been used, including clay,²⁰ metallic sulfides,²¹ and sulfur.²² Since mercaptans may add to olefins

¹⁸ Krainer and Reid, *J. Am. Chem. Soc.*, **43**, 880 (1921).

¹⁹ Borglin and Ott, U. S. pat. 2,052,210 [*C. A.*, **30**, 7089 (1936)]; U. S. pat. 2,076,875 [*C. A.*, **31**, 4017 (1937)].

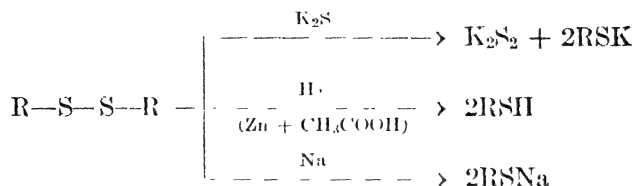
²⁰ Reuter and Gaus, U. S. pat. 2,101,096 [*C. A.*, **32**, 954 (1938)].

²¹ Williams and Allen, U. S. pat. 2,052,268 [*C. A.*, **30**, 7122 (1936)].

²² Jones and Reid, *J. Am. Chem. Soc.*, **60**, 2452 (1938).

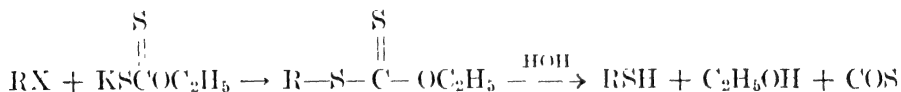
(p. 850), sulfides are by-products of the reaction. Disulfides and paraffin hydrocarbons are other by-products.²¹

Reduction of Disulfides. Disulfides undergo reductive cleavage with potassium sulfide,²³ zinc and acetic acid,²¹ or metallic sodium.²⁵

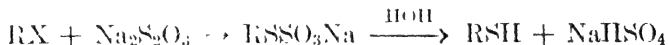


Since the disulfides are generally no more readily available than the mercaptans, this method is of limited usefulness. However, cleavage of disulfides with sodium may be used²⁵ advantageously to prepare sodium mercaptides, in this way avoiding the isolation of mercaptans.

Hydrolysis of Thioesters. Reactive halogen compounds form, with potassium ethyl xanthate, S-alkyl ethyl xanthates which may be hydrolyzed to mercaptans.²⁶



While the salt of any thioacid might be used in this reaction, the xanthates are the most readily available compounds of this type and are almost always employed in laboratory practice. Sodium thiosulfate may also be used²⁷ (p. 862) but reacts more slowly and requires care to avoid the formation of disulfides.



Miscellaneous Methods. Aliphatic sulfonyl chlorides are reduced to mercaptans by the methods used for the preparation of thiophenols (p. 844); this is not useful for the preparation of mercaptans since they are more readily available than the aliphatic sulfonyl chlorides. Mercaptans are formed, along with sulfides and polysulfides, by the action of sulfur on the Grignard reagent (p. 507). Mercaptans are produced

²³ Otto and Rossing, *Ber.*, **19**, 3129 (1886).

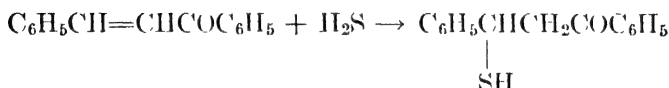
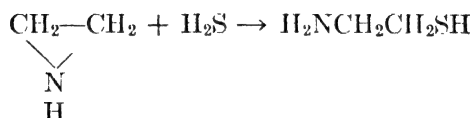
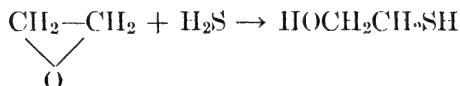
²⁴ Noller and Gordon, *J. Am. Chem. Soc.*, **55**, 1090 (1933).

²⁵ Stutz and Shriner, *ibid.*, **55**, 1242 (1933).

²⁶ Debus, *Ann.*, **72**, 1 (1849); *Ann.*, **75**, 121 (1850); Salomon, *J. prakt. Chem.*, [2] **6**, 433 (1873); Leuckart, *ibid.*, [2] **41**, 179 (1890); Billman, *Ann.*, **339**, 351 (1905); Mauthner, *Ber.*, **39**, 1347 (1906); Tschugaeff and Gasteff, *Ber.*, **42**, 4631 (1909), Zincke and Jorg, *Ber.*, **42**, 3362 (1909); Zincke and Dahm, *Ber.*, **45**, 3457 (1912).

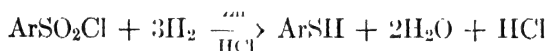
²⁷ Otto and Troeger, *Ber.*, **26**, 996 (1893).

when disulfides are used for the dehydrogenation of cycloparaffins (p. 863). Though alcohols may be converted directly to mercaptans by means of phosphorus pentasulfide,²⁸ this is not a useful preparative method. Ethyl iodide gives ethyl mercaptan²⁹ with aqueous hydrogen sulfide, even in the presence of acid. β -Hydroxymercaptans,³⁰ β -aminomercaptans,³¹ α -aminomercaptans,³² and β -ketomercaptans³³ are obtained by the special methods summarized in the following equations.



Preparation of Thiophenols

Reduction of Sulfonyl Chlorides. The reduction of an aromatic sulfonyl chloride with zinc and aqueous acid^{34a} or with stannous chloride^{34b} is the most common method for the preparation of thiophenols. The yields are generally high (above 90 per cent), and the method is satisfactory unless nitro or other readily reducible groups are present.



From Diazonium Salts. The reaction³⁵ of cold solutions of a diazonium salt and potassium ethyl xanthate forms a diazonium xanthate

²⁸ Pishchimuka, *J. Russ. Phys. Chem. Soc.*, **56**, 11 (1925) [*C. A.*, **19**, 2808 (1925)].

²⁹ Brown and Snyder, *J. Am. Chem. Soc.*, **48**, 1926 (1926).

³⁰ Nenitzescu and Scarlatescu, *Ber.*, **68**, 587 (1935).

³¹ Mills and Bogert, *J. Am. Chem. Soc.*, **62**, 1073 (1940).

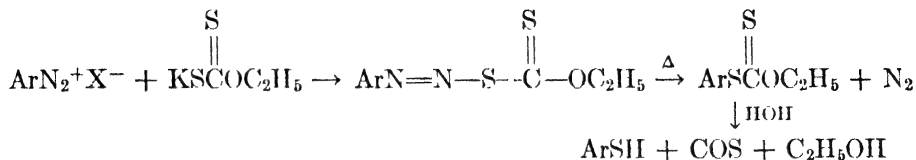
³² Binz and Pence, *ibid.*, **61**, 3134 (1939).

³³ Fromm, Haas, and Hubert, *Ann.*, **394**, 290 (1912); Nicolet, *J. Am. Chem. Soc.*, **57**, 1098 (1935).

³⁴ (a) Adams and Marvel, *Org. Syntheses*, Coll. Vol. I, 490 (1932); Vogt, *Ann.*, **119**, 142 (1861); (b) Bogert and Bartlett, *J. Am. Chem. Soc.*, **53**, 4046 (1931); Suter and Scrutchfield *ibid.*, **58**, 54 (1936).

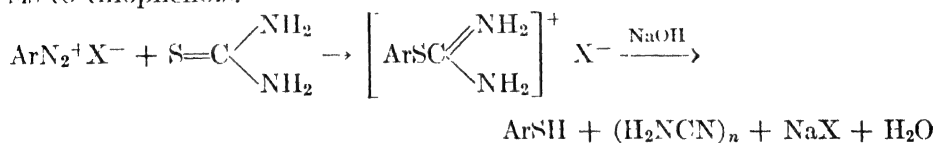
³⁵ Leuckhardt, *Ber.*, **21**, 915 (1888).

which, upon warming, forms an S-aryl ethyl xanthate. Alkaline hydrolysis³⁶ of the last gives a thiophenol.



The reaction is generally mild but occasionally explosions occur³⁶ when the xanthate and diazonium solutions are mixed.

S-Arylisothiuronium salts may be prepared³⁷ by the reaction of diazonium salts with thiourea; these are converted by alkaline hydrolysis to thiophenols.



Similar results may be obtained³⁷ if thiourea is replaced by diphenylthiourea or 1,4-diphenylthiosemicarbazide.

Small yields of thiophenols have been obtained, along with sulfides and disulfides, by the reaction³⁸ of diazonium salts with hydrogen sulfide, sodium sulfide, and sodium thiosulfate.

Other Methods. Thiophenols have been obtained in poor yields by the reaction of phenols with phosphorus pentasulfide³⁹ and by the reaction of aromatic compounds with sulfur in the presence of aluminum chloride.⁴⁰ Thiophenols are formed, along with sulfides and disulfides, by the action of sulfur on the Grignard reagent (p. 508). Aryl halides in which the halogen is activated by the presence of other substituents react with thiourea according to the scheme described earlier (p. 841) for alkyl halides; for example, 2-chloro-5-nitropyridine may be converted to 2-mercapto-5-nitropyridine.⁴¹ The reductive cleavage of disulfides (p. 843) is common to both aromatic and aliphatic derivatives. The hydrolysis of thiourethanes⁴² produces thiophenols. Sulfhydryl compounds are formed by the reduction of thiol sulfonic esters (p. 909).

³⁶ Hantzsch and Freese, *Ber.*, **28**, 3240 (1895).

³⁷ Busch and Schulz, *J. prakt. Chem.*, **150**, 173 (1933).

³⁸ Griess, *Ann.*, **137**, 74 (1866); Grache and Mann, *Ber.*, **15**, 1683 (1882); Stadler, *Ber.*, **17**, 2078 (1884); Klason, *Ber.*, **20**, 349 (1887); Tassinari, *Ber.*, **25**, 908c (1892).

³⁹ Flesch, *Ber.*, **6**, 478 (1873); Fittica, *Ann.*, **172**, 303 (1874).

⁴⁰ Friedel and Crafts, *Ann. chim. phys.*, [6] **14**, 438 (1888); Glass and Reid, *J. Am. Chem. Soc.*, **51**, 3428 (1929).

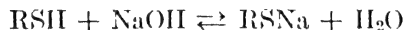
⁴¹ Surrey and Lindwall, *J. Am. Chem. Soc.*, **62**, 1697 (1940).

⁴² v. Braun, *Ber.*, **42**, 4568 (1909).

Reactions of Mercaptans and Thiophenols

With Alkali. Sulfhydryl compounds are considerably more acidic than the corresponding hydroxyl compounds and, as would be expected by analogy with their oxygen analogs, thiophenols are more acidic than mercaptans.

Low-molecular-weight mercaptans and thiophenols dissolve in aqueous alkali with the formation of extensively hydrolyzed mercaptides.



However, sodium methyl mercaptide may be isolated from aqueous solution,⁴³ and the sodium salts of some high-molecular-weight thiophenols are quite insoluble. Mercaptans of high molecular weight are so insoluble in water that the above equilibrium is shifted to the left and these mercaptans are therefore insoluble in aqueous alkali.⁴⁴

In refining gasoline, the removal of mercaptans is based on their solubility in alkali. The naphtha is washed with alkali, removing most of the mercaptans of low molecular weight. The solubility of mercaptans in hydrocarbons, however, shifts the mercaptan-mercaptide equilibrium and some mercaptans, especially those of high molecular weight, remain in the hydrocarbon layer. The method is improved by the addition⁴⁵ of substances such as sodium isobutyrate which increase the solubility of mercaptans in the aqueous layer. Steam distillation of the aqueous mercaptide solution removes the mercaptans, and the alkaline solution remaining may be used again for the treatment of naphtha.⁴⁶

The sodium mercaptides are useful for the synthesis of sulfides (p. 854). Alcoholic alkali may be used for the preparation of mercaptides from mercaptans which are insoluble in aqueous alkali. In reactions which require anhydrous conditions the mercaptides are prepared by the reaction of mercaptans with sodium alkoxides.



With Salts of Heavy Metals. The reaction of a mercaptan or thiophenol with an aqueous solution of the salt of a heavy metal gives a highly insoluble mercaptide. Mercury, lead, zinc, and copper mercaptides have probably been the most widely studied⁴⁷ of compounds of

⁴³ Phillips and Clarke, *J. Am. Chem. Soc.*, **45**, 1755 (1923).

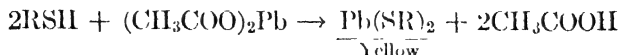
⁴⁴ Yabroff, *Ind. Eng. Chem.*, **32**, 257 (1940).

⁴⁵ Yabroff, Berkeley and White, U. S. pat. 2,149,379 [*C. A.*, **33**, 4412 (1939)]; U. S. pat. 2,149,380 [*C. A.*, **33**, 4412 (1939)]; Yabroff and White, *Ind. Eng. Chem.*, **32**, 950 (1940).

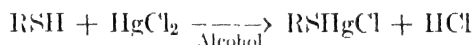
⁴⁶ Birch and Norris, *J. Chem. Soc.*, **127**, 898 (1925).

⁴⁷ Wertheim, *J. Am. Chem. Soc.*, **51**, 3661 (1929); Sachs, Schlesinger, and Antoine, *Ann.*, **433**, 154 (1923); Bertram, *Ber.*, **25**, 63 (1892); Klason, *Ber.*, **20**, 3412 (1887).

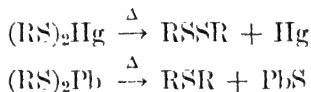
this type, but many others (silver, gold, platinum, palladium, iridium, nickel, iron, cobalt, tin, and cadmium mercaptides) have been prepared.⁴⁸



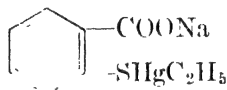
The mercaptides are covalent compounds, insoluble in water and soluble in organic solvents. Some of them are so readily formed* and so insoluble in water that they are precipitated even when a strong acid is the other product (e.g., the reaction of a mercaptan with silver nitrate). However, in order to insure complete precipitation of the mercaptide, the acid is neutralized or the reaction carried out with the metallic salt of a weak acid (mercuric cyanide, mercuric oxide, lead acetate, etc.). When polyvalent metals are used, the intermediate expected from the stepwise reaction of the mercaptan with the salt may sometimes be obtained. For example, alkylmercaptomercuric chlorides may be obtained from the reaction of mercaptans with mercuric chloride in alcohol solution.^{49, 50}



The lead mercaptides from the higher mercaptans are soluble in gasoline⁵¹ but are converted by atmospheric oxygen to insoluble peroxides.⁵² The mercaptides of heavy metals may be used in metathetical reactions in the same way as the sodium mercaptides. The mercury and lead mercaptides differ in their behavior upon pyrolysis; the former give disulfides and the latter sulfides.⁵³



An unsymmetrical mercury mercaptide, "merthiolate," is used as a germicide.



⁴⁸ Manchot and Davidson, *Ber.*, **62**, 684 (1929); Wuyts and Vangindertaelen, *Bull. soc. chim. Belg.*, **30**, 323 (1921) [*C. A.*, **16**, 5077 (1922)]; Ray, *J. Chem. Soc.*, **115**, 871 (1919); *ibid.*, **123**, 133 (1923); Hermann, *Ber.*, **38**, 2813 (1905); Klason, *J. prakt. Chem.*, [2] **67**, 1 (1903); Hofmann and Kabe, *Z. anorg. Chem.*, **14**, 293 (1897); Willgerodt, *Ber.*, **18**, 331 (1885).

* The name "mercaptan" results from the ready reaction of this series with mercury salts ("corpus mercurius captans").

⁴⁹ Debus, *Ann.*, **72**, 18 (1939); Gerlich, *Ann.*, **178**, 88 (1875); Ray, *J. Chem. Soc.*, **115**, 871 (1919).

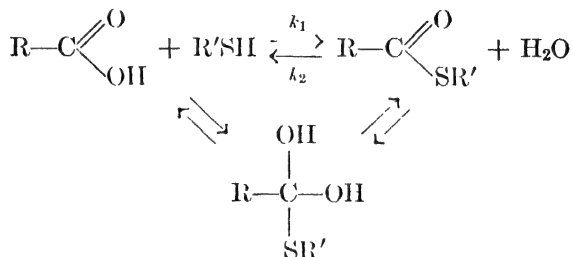
⁵⁰ Rawlings, *J. Chem. Soc.*, 868 (1937); Frederick and Challenger, *ibid.*, 1872 (1938).

⁵¹ Fore and Bost, *J. Am. Chem. Soc.*, **59**, 2557 (1937).

⁵² Ott and Reid, *Ind. Eng. Chem.*, **22**, 884 (1930).

⁵³ Otto, *Ber.*, **13**, 1289 (1880).

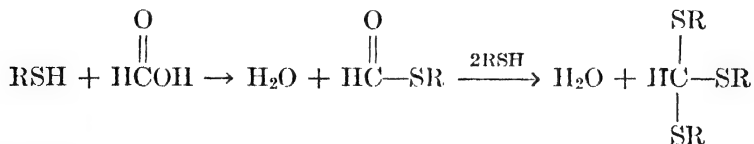
With Carboxylic Acids. The reaction⁵⁴ of mercaptans and thiophenols with carboxylic acids other than formic acid is analogous to the esterification of alcohols. Assuming that the mercaptans, like the alcohols,⁵⁵ react initially by addition to the double bond of the carboxyl group, it is understandable that the products are thioesters and water, rather than esters and hydrogen sulfide.



The reaction is reversible and the equilibrium unfavorable for the formation of thioesters in good yields. For example, in the reaction of ethyl mercaptan with benzoic acid the velocity constant (k_1) of the esterification reaction is one thirty-second of that of the hydrolysis reaction (k_2). In this case, the equilibrium mixture from equimolar quantities of the reactants contains only 15 per cent ethyl thiolbenzoate.⁵⁶ In the corresponding esterification with ethyl alcohol and benzoic acid, k_1 is about four times k_2 and at equilibrium about 67 per cent of the reactants have been converted to ethyl benzoate. It may be noted that the above mechanism agrees with the observation (p. 936) that thioacids react with alcohols to give esters and hydrogen sulfide.

The primary mercaptans give approximately the same yields of thioesters with the exception of methyl mercaptan, which gives slightly higher yields.⁵⁷ The difference in reactivity⁵⁸ between primary and secondary mercaptans is similar to the difference between primary and secondary alcohols.

The reaction of formic acid with mercaptans and thiophenols does not stop with the formation of a thiolformate; the products are trithioorthoformates.⁵⁹



⁵⁴ Faber and Reid, *J. Am. Chem. Soc.*, **39**, 1930 (1917).

⁵⁵ Roberts and Urey, *ibid.*, **60**, 2391 (1938); *ibid.*, **61**, 2584 (1939); Datta, Day, and Ingold, *J. Chem. Soc.*, 838 (1939); Hughes, Ingold, and Masterman, *ibid.*, 840 (1939).

⁵⁶ Reid, *Am. Chem. J.*, **43**, 489 (1910).

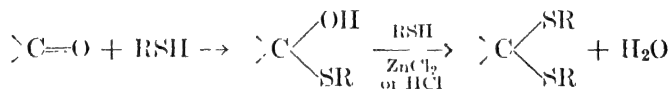
⁵⁷ Pratt and Reid, *J. Am. Chem. Soc.*, **37**, 1934 (1915).

⁵⁸ Kimball and Reid, *ibid.*, **38**, 2757 (1916).

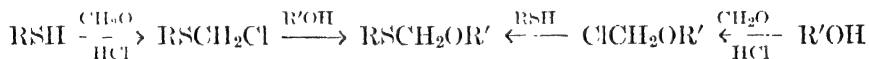
⁵⁹ Holmberg, *Ann.*, **353**, 131 (1907).

The carboxylic acid chlorides (but not sulfonyl chlorides [p. 907]) react normally with mercaptans and thiophenols, giving thioesters (p. 932).

With Aldehydes and Ketones. The reaction of sulfhydryl compounds with the carbonyl group is analogous to the formation of acetals from alcohols but two important differences may be emphasized: (1) Sulfhydryl compounds have a much greater reactivity than hydroxyl compounds in addition reactions. Although the phenols do not react with carbonyl compounds to form acetals or ketals and although alcohols seldom give ketals directly by reaction with ketones (p. 653), thiophenols and mercaptans react with both aldehydes and ketones. (2) The products obtained from sulfhydryl compounds are much more stable than acetals and ketals. Mercaptals and mercaptols are not readily hydrolyzed by acid and are stable toward alkali.



The products obtained from aldehydes are known as *mercaptals*, and those from ketones as *mercaptols*. The initial product of the reaction is a hemimercaptal (or hemimercaptol) which reacts with another mole of sulfhydryl compound spontaneously or in the presence of a catalyst⁶⁰ to give the mercaptal (or mercaptol). Hemimercaptols have been obtained from the quinones derived from the polynuclear aromatic hydrocarbons,⁶¹ from chloral, from alloxan,⁶² and from formaldehyde⁶³ (monothiohemiformals). Monothioformals may be prepared⁶⁴ from α -chloromethyl sulfides or ethers.



Dimercaptols are formed by the reaction of mercaptans with both carbonyl groups of diacetyl, acetylacetone and acetonylacetone, but in other 1,2 and 1,3-diketones only one carbonyl group reacts.⁶⁵ Mercaptals and mercaptols may be prepared⁶⁶ from aldehyde and ketone sugars by reaction with mercaptans in the presence of hydrochloric acid. The

⁶⁰ Baumann, *Ber.*, **18**, 884 (1885); **19**, 2803 (1886); Posner, *Ber.*, **36**, 296 (1903); *Ber.*, **32**, 1239 (1899); Autenrieth, *Ann.* **259**, 365 (1890); *Ber.*, **24**, 166 (1891).

⁶¹ Schönberg, Schutz, Arend, and Peter, *Ber.*, **60**, 2344 (1927).

⁶² d'Ouville, Myers, and Connor, *J. Am. Chem. Soc.*, **61**, 2033 (1939).

⁶³ Levi, *Gazz. chim. ital.*, **62**, 775 (1932).

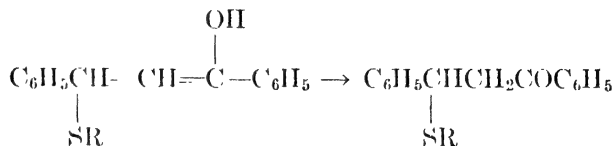
⁶⁴ Bohme, *Ber.*, **69**, 1610 (1936); Wenzel and Reid, *J. Am. Chem. Soc.*, **59**, 1090 (1937).

⁶⁵ Posner, *Ber.*, **33**, 2983 (1900); *Ber.*, **35**, 503 (1902).

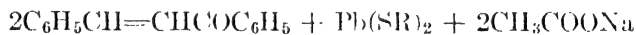
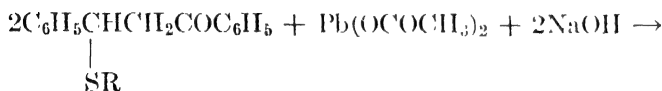
⁶⁶ Fischer, *Ber.*, **27**, 673 (1884); Lawrence, *Ber.*, **29**, 547 (1890); Fischer, Helferich, and Ostman, *Ber.*, **53**, 873 (1920); Uyeda, *Bull. Chem. Soc. Japan.*, **4**, 264 (1929).

products are readily crystallized, not very soluble in water, and have been useful in sugar chemistry (p. 1575).

With α,β -Unsaturated Ketones, Acids, and Esters. Mercaptans and thiophenols react ⁶⁷ with α,β -unsaturated ketones, esters, and acids, giving β -alkylthio derivatives (presumably by 1,4-addition).



In some cases the reaction occurs without a catalyst, in others piperidine or sodium ethoxide is necessary. The above reaction may be reversed by treatment with a base in the presence of lead acetate.



With Olefins.⁶⁸ Although hydrogen sulfide adds to olefins (p. 842) in accordance to Markownikoff's rule ("normal addition"), most of the reactions reported for mercaptans and thiophenols occur in the manner contrary to this rule ^{69, 72} ("abnormal addition"). The apparent contradictions concerning the mode of addition which appear in the older literature are a result of an incomplete understanding of the factors influencing the addition. Addition in the fashion opposite to that expected from Markownikoff's rule is catalyzed by peroxides,^{22, 70} light,⁷¹ and phosphoric acid.⁷² Ordinary samples of hydrocarbons and thiophenols appear ²² to contain enough peroxides to bring about this reaction. No addition occurs with carefully purified reagents;²² in the presence of sulfur ²² (as ethyl tetrasulfide) or sulfuric acid ⁷² (diluted with water or acetic acid) reaction occurs in accordance with Markownikoff's rule.

⁶⁷ Nicolet, *J. Am. Chem. Soc.*, **53**, 3066 (1931); *ibid.*, **57**, 1098 (1935); Morgan and Friedman, *Biochem. J.*, **32**, 733 (1938).

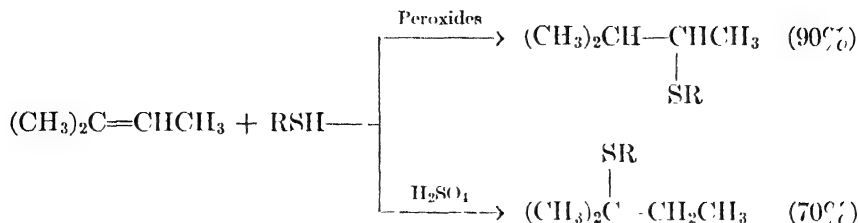
⁶⁸ For a more complete review of this subject, see Mayo and Walling, *Chem. Rev.*, **27**, 351 (1940).

⁶⁹ Posner, *Ber.*, **38**, 646 (1905); Ashworth and Burkhardt, *J. Chem. Soc.*, 1791 (1928).

⁷⁰ Kharasch, Read, and Mayo, *Chem. and Ind.*, 752 (1938).

⁷¹ Carothers, *J. Am. Chem. Soc.*, **55**, 2008 (1933).

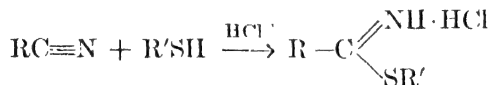
⁷² (a) Ipatieff, Pines, and Friedman, *ibid.*, **60**, 2731 (1938); (b) Ipatieff and Friedman *ibid.*, **61**, 71 (1939).



Addition to acetylenes will also occur,⁷³ but there are indications⁷¹ that it may not take place as readily as with olefins.

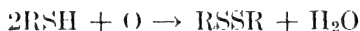


With Nitriles. Imino thioesters are formed by the reaction of mercaptans and thiophenols with nitriles⁷⁴ in the presence of dry hydrogen chloride.



Solid derivatives suitable for the identification of cyanides are obtained by the reaction of mercaptoacetic acid with cyanides.⁷⁵

With Oxidizing Agents. Compounds containing the sulfhydryl group are readily oxidized to disulfides and, by strong oxidizing agents, to other products (pp. 862, 888, 907).



Such varied reagents as halogens, hypohalites, nitric acid, concentrated sulfuric acid, potassium permanganate, potassium ferrieyanide, sulfuryl chloride, ferric chloride, sodium polysulfide, "positive" halogen compounds (p. 854), sulfur dioxide, and atmospheric oxygen constitute a partial list of the substances which oxidize mercaptans and thiophenols. Oxidation by air occurs very readily, especially in alkaline solution. Though the oxidation of sulfhydryl compounds to disulfides will be discussed later (p. 861), it may be noted that the use of iodine as the oxidizing agent for this reaction has been adapted to the quantitative determination of these compounds.⁷⁶ Elementary sulfur⁷⁷ also causes the oxidation of sulfhydryl compounds.

⁷³ Kohler and Potter, *ibid.*, **57**, 1316 (1935); Fr. pat. 777,427 [*C. A.*, **29**, 4024 (1935)]; Ger. pat. 617,543 [*C. A.*, **30**, 733 (1936)].

⁷⁴ Autenrieth and Bruning, *Ber.*, **36**, 3464 (1903); Pinner and Klein, *Ber.*, **11**, 762 (1878).

⁷⁵ Condo, Hinkel, Fassero, and Shriner, *J. Am. Chem. Soc.* **59**, 230 (1937).

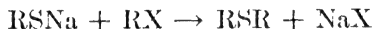
⁷⁶ Sampey and Reid, *ibid.*, **54**, 3404 (1932).

⁷⁷ Holmberg, *Ann.*, **359**, 81 (1908).

—CH=CH—are isosteric and there are many striking similarities in the chemical, physical, and physiological properties of isosteres containing these structures.

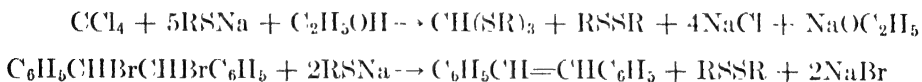
Preparation

By Alkylation. The reaction of mercaptides with alkylating agents (alkyl halides, alkyl sulfates, sodium alkyl sulfates, or alkyl sulfonates ⁸⁶) is analogous to the Williamson synthesis of ethers but occurs much more readily.

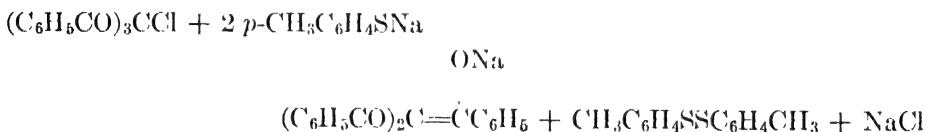


Alcohol is usually a good solvent for the reactants and is frequently used as the reaction medium (*cf.* p. 846).

Polyhalogen compounds ^{59, 87} such as methylene halides, ²⁵ dichloroacetamide, ^{93a} chloroform, 1,1,2-trichloroethane, ethylene halides, acetylene dichloride, and acetylene tetrachloride behave normally in this reaction, with complete replacement of the halogens by alkylthio groups. Carbon tetrachloride ⁸⁸ and some alkylene halides ⁸⁹ cause oxidation of the mercaptide to disulfide.



Instead of undergoing metathesis, compounds containing "positive" halogen may oxidize the mercaptide to disulfide. For example, tribenzoylmethyl chloride ⁹⁰ and sodium *p*-tolylmercaptide give the sodium salt of tribenzoylmethane and di-*p*-tolyl disulfide.



Other halogen compounds which may cause oxidation of mercaptides include ethyl α -chloroacetoacetate, ⁹¹ phenacyl chloride, ⁹⁰ bromonitro-

⁸⁶ Gilman and Beaber, *J. Am. Chem. Soc.*, **47**, 1449 (1925).

⁸⁷ Gabriel, *Ber.*, **10**, 185 (1877); Otto, *Ber.*, **27**, 3055 (1894); Otto, *J. prakt. Chem.*, [2] **51**, 285 (1895); Otto and Muhle, *Ber.*, **28**, 1120 (1895); Fromm, Benzinger, and Schafer, *Ann.*, **394**, 325 (1912); Fromm and Siebert, *Ber.*, **55**, 1014 (1922); Fromm and Landmann, *Ber.*, **56**, 2290 (1923); Kohler and Tishler, *J. Am. Chem. Soc.*, **57**, 223 (1935); du Vigneaud and Patterson, *J. Biol. Chem.*, **114**, 533 (1936).

⁸⁸ Backer and Stedehouder, *Rec. trav. chim.*, **52**, 437 (1935).

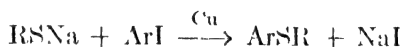
⁸⁹ Otto, *Ber.*, **23**, 1051 (1890); Otto and Muhle, *J. prakt. Chem.*, [2] **51**, 517 (1895); Otto *ibid.*, [2] **53**, 1 (1896).

⁹⁰ Kohler and Potter, *J. Am. Chem. Soc.*, **58**, 2166 (1936).

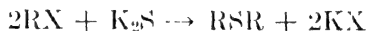
⁹¹ Finger and Hemmeter, *J. prakt. Chem.*, **79**, 449 (1909).

methane,⁹² α -bromo amides,^{93a} α -sulfonyl- α -halo-amides,^{93b, c} and α -bromosulfones.⁹⁴ The oxidation reaction is favored by high temperatures; metathesis may sometimes be made the main reaction⁹³ by operating at room temperature or lower.

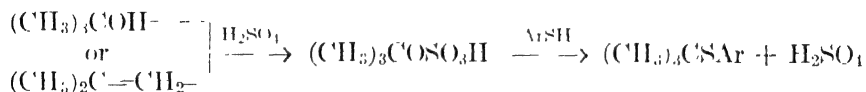
While aryl halides which lack activating groups do not undergo metathesis with sodium mercaptides under ordinary conditions, *p*-nitrochlorobenzene^{16a} and 2,4-dinitrochlorobenzene⁹⁵ react to give sulfides. It has been reported that sulfides are formed by the reactions of aryl bromides with lead mercaptides,⁹⁶ and of aryl iodides with sodium mercaptides in the presence of copper.⁹⁷



The preparation of symmetrical sulfides may be carried out successfully by the action of alkylating agents on sodium or potassium sulfide.^{16c, 98}



The conversion of thiophenols to sulfides may be accomplished in the presence of sulfuric acid, using tertiary alcohols or olefins as alkylating agents.^{72a, 99}



From Olefins. The formation of sulfides from olefins by the addition of hydrogen sulfide, mercaptans, and thiophenols has already been discussed (pp. 843, 850) and needs no further mention.

Sulfur chloride (S_2Cl_2) reacts with olefins by addition to two equivalents of the unsaturated compound. Though the mechanism of the reaction is obscure, it appears to involve two stages¹⁰⁰ and it is likely that sulfur dichloride (SCl_2) is the reactive agent.¹⁰¹ The fate of the

⁹² Mel'nikov, *J. Gen. Chem. (U.S.S.R.)*, **7**, 1546 (1937) [*C. A.*, **31**, 8504 (1937)].

⁹³ (a) d'Ouville and Connor, *J. Am. Chem. Soc.*, **60**, 33 (1938), (b) Ziegler and Connor, *ibid.*, **62**, 1049 (1940); (c) Barr, Ziegler, and Connor, *ibid.*, **63**, 105 (1941).

⁹⁴ Ziegler and Connor, *ibid.*, **62**, 2596 (1940).

⁹⁵ Bost, Turner, and Norton, *ibid.*, **54**, 1985 (1932).

⁹⁶ Bourgeois, *Ber.*, **28**, 2312 (1895); Kraft and Bourgeois, *Ber.*, **23**, 3045 (1890).

⁹⁷ Mauthner, *Ber.*, **39**, 3593 (1906).

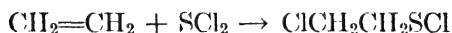
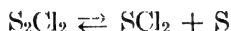
⁹⁸ Cahours and Hofmann, *Ann.*, **102**, 291 (1857).

⁹⁹ Lee, U. S. pat. 2,020,421 [*C. A.*, **30**, 489 (1936)].

¹⁰⁰ Conant, Hartshorn, and Richardson, *J. Am. Chem. Soc.*, **42**, 585 (1920).

¹⁰¹ Patrick and Hackerman, *J. Phys. Chem.*, **40**, 679 (1930); Cooley and Yost, *J. Am. Chem. Soc.*, **62**, 2474 (1940).

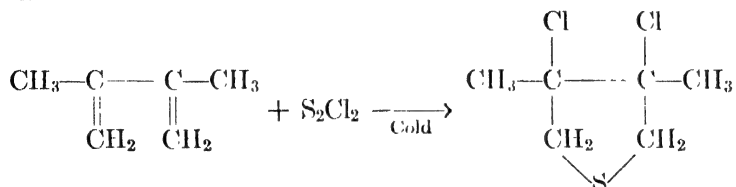
extra sulfur is uncertain,¹⁰² but some of it is present as disulfide and trisulfide. This reaction was used¹⁰³ by the Allies in the war of 1914-1918 for the conversion of ethylene to mustard gas.



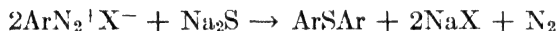
The mechanism indicated for this reaction suggests that sulphenyl chlorides should be capable of reacting with olefins; examples of this have been noted¹⁰⁴ but not extensively investigated.



The reaction of sulfur chloride (S_2Cl_2) with dimethylbutadiene and isoprene occurs by 1,4-addition;¹⁰⁵ butadiene is chlorinated by this reagent.



From Diazonium Salts. Symmetrical aryl sulfides may be obtained by¹⁰⁶ the reaction of diazonium salts with sodium sulfide or sodium thiosulfate. Thiophenols¹⁰⁷ and disulfides¹⁰⁸ may be by-products of the reaction.



Unsymmetrical diaryl sulfides or alkyl aryl sulfides may be obtained¹⁰⁹ by the reaction of diazonium salts with the sodium salts of thiophenols or mercaptans. The products are diazosulfides, which upon heating in alcohol solution decompose to give sulfides.



¹⁰² Felsing, Arenson, and Kopp, *Ind. Eng. Chem.*, **12**, 1054 (1920); Markevich, *Colloid J. (U.S.S.R.)*, **2**, 425 (1926) [*C. A.*, **30**, 7011 (1936)].

¹⁰³ Felsing and Arenson, *Ind. Eng. Chem.*, **12**, 1065 (1920); Gibson and Pope, *J. Chem. Soc.*, **117**, 271 (1920); Green, *J. Soc. Chem. Ind.*, **38**, 469 (1919); *ibid.*, **39**, 363 (1920).

¹⁰⁴ Lecher *et al.*, *Ber.*, **55**, 1474 (1922).

¹⁰⁵ Backer and Strating, *Rec. trav. chim.*, **54**, 52 (1935).

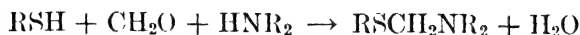
¹⁰⁶ Griess, *Ann.*, **137**, 74 (1866); Stadler, *Ber.*, **17**, 2078 (1884); Klason, *Ber.*, **20**, 349 (1887); Tassinari, *Ber.*, **25**, 908 (1892).

¹⁰⁷ Graebe and Mann, *Ber.*, **15**, 1683 (1882).

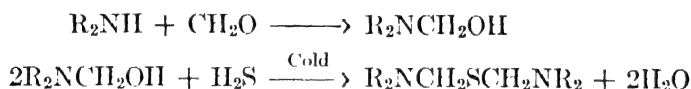
¹⁰⁸ Purgotti, *Gazz. chim. ital.*, **20**, 24 (1890).

¹⁰⁹ Stadler, *Ber.*, **17**, 2075 (1884); Ziegler, *Ber.*, **23**, 2469 (1890); U. S. pat., 2,011,582 [*C. A.*, **30**, 489 (1936)].

From Aldehydes and Ketones. The mercaptals, mercaptols, trithio-orthoformates (pp. 848-9) and the cyclic trimers of thioaldehydes and thioketones (p. 923) are sulfides which are prepared by methods described elsewhere. α -Dialkylaminosulfides may be obtained in good yields ^{10a} by the reaction of mercaptans and secondary amines with formaldehyde.

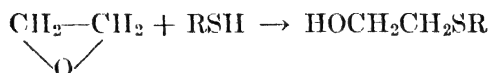
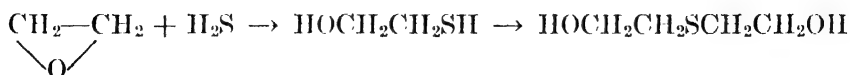
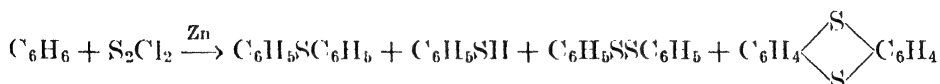
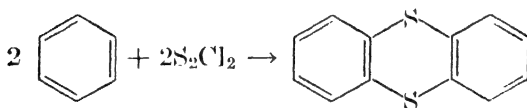
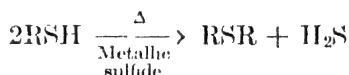


α, α' -Di-(dialkylamino)-sulfides are formed ³² by the reaction of hydrogen sulfide with methylol amines obtained from formaldehyde and secondary amines.



The formation of α -chloromethylsulfides from mercaptans, formaldehyde, and hydrogen chloride has been mentioned previously (p. 849).

Other Methods. Sulfides are formed by the thermal decomposition of lead mercaptides (p. 847), the replacement of the $-\text{SO}_3\text{Na}$ group in certain aromatic sulfonates (p. 895), and the introduction of the $\text{RS}-$ group into active methylene compounds by the use of thiolsulfonic esters (p. 910) or sulfenyl chlorides (p. 923); these methods are discussed elsewhere. Sulfides may also be obtained (1) catalytically ¹¹⁰ from mercaptans in the presence of a metallic sulfide catalyst at high temperatures, (2) from aromatic hydrocarbons and chlorides of sulfur, ¹¹¹ and (3) from the reaction of ethylene oxide with hydrogen sulfide, ³⁰ mercaptans, ¹¹² or thiophenols.



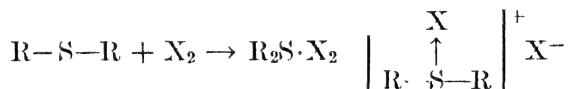
¹¹⁰ Sabatier and Mailhe, *Compt. rend.*, **150**, 1569 (1910).

¹¹¹ Krafft and Lyons, *Ber.*, **29**, 435 (1896); Schmidt, *Ber.*, **11**, 1168 (1878); Friedländer and Simon, *Ber.*, **55**, 3969 (1922); Wood and Fieser, *J. Am. Chem. Soc.*, **62**, 2674 (1940)

¹¹² Fromm and Jörg, *Ber.*, **58**, 304 (1925).

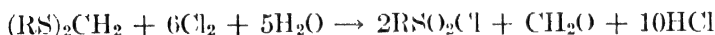
Reactions

With Halogens. Under anhydrous conditions sulfides react with chlorine,¹¹³ bromine,^{113, 114} or iodine¹¹⁵ to form dihalide addition products. These products may be considered molecular compounds, or as having a structure similar to that of sulfonium salts (p. 419).

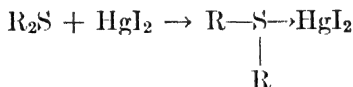


The formation of dihalides occurs with great ease¹¹⁶ when methyl or methylene groups are adjacent to sulfur. The reaction with bromine takes place so readily that it has been used¹¹⁷ as a quantitative method for the determination of sulfides. The reaction of halogens with aryl sulfides¹¹³ must be carried out below 0° to avoid nuclear halogenation.

In the presence of water the simple sulfides are oxidized by halogens to sulfoxides,¹¹³ probably by formation of the dihalide, followed by hydrolysis (p. 871). If the reaction is carried to completion, sulfones are formed.¹¹⁸ Under these conditions compounds containing two sulfide linkages attached to the same carbon atom¹¹⁹ (mercaptals, trimeric thioaldehydes, etc.) may be cleaved with the formation of sulfonyl chlorides.



With Inorganic Salts. The sulfides form addition compounds¹²⁰ with salts of the heavy metals such as mercury, platinum, palladium, and gold. Probably these form as a result of the donor activity of sulfur, and the products obtained from mercuric iodide,¹²¹ for example, may be represented as follows.



¹¹³ Fries and Vogt, *Ann.*, **381**, 337 (1911).

¹¹⁴ Chelintzev, *J. Russ. Phys. Chem. Soc.*, **44**, 1885 (1913).

¹¹⁵ Paton, *Bull. soc. chim.*, **50**, 201 (1888).

¹¹⁶ Fromm and Raiziss, *Ann.*, **374**, 90 (1910).

¹¹⁷ Sampey, Slagle, and Reid, *J. Am. Chem. Soc.*, **54**, 3401 (1932).

¹¹⁸ Boeseken, *Rec. trav. chim.*, **29**, 315 (1910).

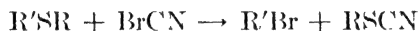
¹¹⁹ Lee and Dougherty, *J. Org. Chem.*, **5**, 81 (1940).

¹²⁰ Loir, *Ann.*, **87**, 369 (1853); *Ann. chim. phys.*, [3] **39**, 441 (1853); Blomstrand, *J. prakt. Chem.*, [2] **38**, 525 (1888); Faragher, Morrell, and Comay, *J. Am. Chem. Soc.*, **51**, 2774 (1929).

¹²¹ Phillips, *J. Am. Chem. Soc.*, **23**, 250 (1901).

These addition compounds are usually solids. Those obtained with mercuric chloride have been useful¹²² in the isolation of sulfides from petroleum distillates; the alkyl sulfides may be recovered by treatment of the addition products with hydrogen sulfide. Solid products obtained by reaction with palladous chloride¹²³ have been used for the identification of sulfides.

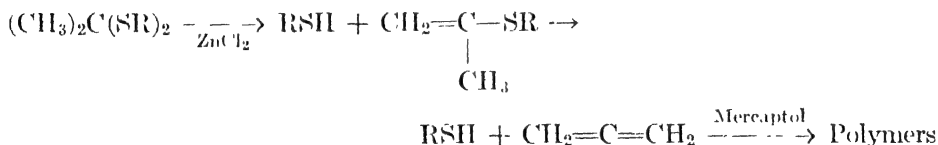
With Cyanogen Bromide. The cleavage of sulfides by cyanogen bromide¹²⁴ is analogous to the cleavage of the amines with this reagent. The products obtained from unsymmetrical sulfides depend upon the "relative electronegativities" (p. 1072) of the groups; if both are saturated alkyl groups the smaller radical appears predominantly as the bromide.



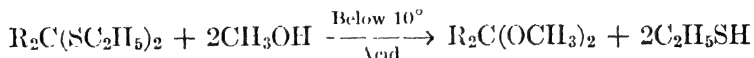
Other Reactions. The reactions of sulfides with alkyl halides. (p. 867) and with oxidizing agents (pp. 870, 874) are discussed elsewhere. Sulfides form addition products with hexaphenylethane.¹²⁵ The hydrogen attached to the α -carbon in sulfides is more acidic¹²⁶ than in the corresponding ethers; this is shown by the observation that methyl phenyl sulfide undergoes metalation of the methyl group, whereas anisole gives ring metalation.



The pyrolysis of mercaptols^{127a} is reported to give vinyl sulfides and polymers; the latter are said to be formed from allenes.



Mercaptols react with alcohols at low temperatures under the influence of acids, giving^{127b} acetals and mercaptans.



¹²² Mabery and Smith, *Am. Chem. J.*, **13**, 232 (1891); McKittrick, *Ind. Eng. Chem.*, **21**, 585 (1929).

¹²³ Ipatieff and Friedman, *J. Am. Chem. Soc.*, **61**, 684 (1939).

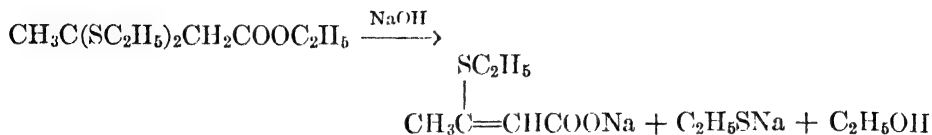
¹²⁴ v. Braun and Engebertz, *Ber.*, **56**, 1573 (1923).

¹²⁵ Rogers and Dougherty, *J. Am. Chem. Soc.*, **50**, 149 (1928).

¹²⁶ Gilman and Webb, *ibid.*, **62**, 987 (1940).

¹²⁷ (a) Sporzynski, *Arch. Chem. Farm.*, **3**, 59 (1936) [*C. A.*, **32**, 8359 (1938)]; (b) Mochel U. S. pat. 2,229,665 [*C. A.*, **35**, 2905 (1941)].

Whereas the sulfide link is quite stable in the simple sulfides, sulfides with a labilizing group in the β -position are readily cleaved in the presence of alkali. An example of this has been noted (p. 850) in the regeneration of benzalacetophenone from its addition product with thio-cresol; other examples ¹²⁸ are found in the cleavage of mercaptols derived from β -keto esters.



The reactions of certain sulfides indicate that sulfur may expand its valence shell (p. 881) and in this way cause activation of the methylene group.

Mustard Gas and Related Compounds

β,β' -Dichloroethyl sulfide ("mustard gas") is a strong vesicant. Individuals differ considerably in sensitivity, but approximately 0.5 mg. of mustard gas per square centimeter of skin produces blisters.¹²⁹ Animals are killed ¹²⁹ after eight hours' exposure to air containing less than 0.01 mg. of mustard gas per liter, although death may be delayed for several days. "Sesqui-mustard" ($\text{ClCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{Cl}$) is a stronger vesicant ¹³⁰ than mustard gas. β,β' -Dibromoethyl sulfide ¹³¹ is similar in action but has a lower vapor pressure than mustard gas and is less dangerous to handle. Branching of the carbon chain ¹³² and increasing the molecular weight diminish the vesicant activity of β -halo-sulfides; $(\text{CH}_3\text{CHClCH}_2)_2\text{S}$ is much less toxic than mustard gas, and $(\text{CH}_3\text{CHClCH}(\text{CH}_3))_2\text{S}$ is practically inactive. β -Monochloroalkyl sulfides ¹³³ and α,α' -dichloroalkyl sulfides ¹³⁴ are relatively weak vesicants. β,β' -Dichlorovinyl sulfide ¹³⁵ ($\text{ClCH}=\text{CH}$)₂S has a nauseating odor but is not a strong vesicant. The vesicant action of mustard gas and related compounds is destroyed ¹³⁶ by oxidation or chlorination.

¹²⁸ Posner, *Ber.*, **32**, 2802, 2805 (1899); *Ber.*, **34**, 2643 (1901).

¹²⁹ Marshall and Lynch, *J. Pharmacol.*, **12**, 291 (1918); Marshall, *J. Am. Med. Assoc.*, **73**, 684 (1919).

¹³⁰ Bennett and Whincop, *J. Chem. Soc.*, **119**, 1860 (1921); Rosen and Reid, *J. Am. Chem. Soc.*, **44**, 634 (1922).

¹³¹ Steinkopf, Herold, and Stöhr, *Ber.*, **53**, 1007 (1920).

¹³² Pope and Smith, *J. Chem. Soc.*, **119**, 396 (1921).

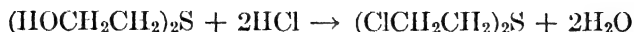
¹³³ Demuth and Meyer, *Ann.*, **240**, 305 (1884).

¹³⁴ Mann and Pope, *J. Chem. Soc.*, **123**, 1172 (1923); Ruigh and Erickson, *J. Am. Chem. Soc.*, **61**, 915 (1939).

¹³⁵ Müller and Metzger, *J. prakt. Chem.*, [2] **114**, 123 (1926).

¹³⁶ Desgrez, Guillemard, and Labat, *Chimie und Industrie*, **6**, 942 (1921); Spica, *Gazz chim. ital.*, **49**, 11, 299 (1919); Helfrich and Reid, *J. Am. Chem. Soc.*, **42**, 1208 (1920).

The preparation of mustard gas by the reaction of ethylene with sulfur chloride has already been mentioned (p. 855). During the war of 1914–1918 it was prepared in Germany¹³⁷ by passing hydrogen chloride into a solution of β,β' -dihydroxyethyl sulfide in hydrochloric acid.



IV. DISULFIDES

General Characteristics

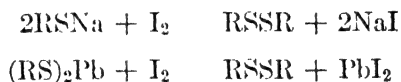
The disulfides have higher boiling points than the corresponding mercaptans, and their odors, though disagreeable, are not so objectionable as those of the sulfhydryl compounds. Allyl propyl disulfide is present in onions¹³⁸ and occurs, along with diallyl disulfide and allyl sulfide, in oil of garlic.¹³⁸ 1-Propenyl *sec.*-butyl disulfide ($\text{CH}_3\text{CH}_2\text{CH}=\text{CH}-\text{S}-\text{S}-\text{CH}(\text{CH}_3)_2$) has been isolated from oil of



asafetida.¹³⁹ Disulfides may produce symptoms similar to those observed in ivy poisoning; the response of individuals varies greatly, but this effect is usually noted after the skin has been repeatedly in direct contact with disulfides.

Preparation

Oxidation of Mercaptans and Thiophenols. The ease of oxidation of sulfhydryl compounds has been discussed elsewhere (p. 851). For the preparation of disulfides it is necessary to select an oxidizing agent which will not oxidize disulfides. Convenient laboratory methods are the reaction of a sulfhydryl compound in aqueous alkali with iodine¹⁴⁰ and reaction of a lead mercaptide with iodine.^{16a}



Ferric chloride,¹⁴¹ lead peroxide,¹⁴² hydrogen peroxide,¹⁴³ and copper sulfate¹⁴⁴ also appear to be well suited for use in preparative work.

¹³⁷ Carr, *J. Soc. Chem. Ind.*, **38R**, 468 (1919).

¹³⁸ Semmler, *Arch. Pharm.*, **230**, 434 (1892).

¹³⁹ Mannich and Fresenius, *ibid.*, **274**, 461 (1936).

¹⁴⁰ Smythe, *J. Chem. Soc.*, **95**, 349 (1909).

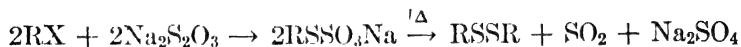
¹⁴¹ Zincke and Frohneberg, *Ber.*, **43**, 840 (1910).

¹⁴² Pummerer, *Ber.*, **43**, 1401 (1910); Zincke and Frohneberg, *Ber.*, **42**, 2721 (1909).

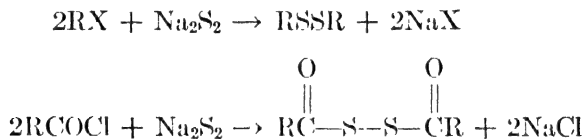
¹⁴³ Ritter and Sharpe, *J. Am. Chem. Soc.*, **59**, 2351 (1937).

¹⁴⁴ Klason, *Ber.*, **20**, 3407 (1887); Loven, *J. prakt. Chem.*, [2] **29**, 366 (1864).

Reaction of Alkylating Agents with Sodium Thiosulfate. Sodium alkyl thiosulfates, obtained by the reaction of alkyl halides with sodium thiosulfate, are converted to disulfides by heating.¹⁴⁵

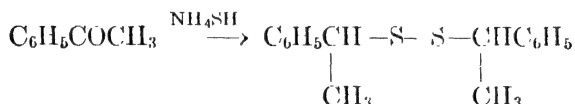


Reaction of Alkylating Agents with Sodium Disulfide. Disulfides are obtained by the reaction¹⁴⁶ of alkyl halides or sodium alkyl sulfates with a solution of sodium sulfide in which an equivalent amount of free sulfur has been dissolved. When this reagent is treated with acyl chlorides, acyl disulfides¹⁴⁷ are formed.



Sodium disulfide solution appears to be an equilibrium mixture containing, in addition to disulfide, sodium sulfide and sodium polysulfides. As a consequence, alkyl sulfides and polysulfides are by-products from the preparation of alkyl disulfides by this method.

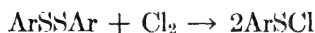
Other Methods. The action of ammonium hydrosulfide on ketones (p. 926) has been reported¹⁴⁸ to reduce the carbonyl group with formation of the corresponding disulfide; the reaction has not been extensively studied.



As mentioned elsewhere, thermal decomposition of mercuric mercaptides (p. 847), the action of sodium sulfide on diazonium salts (p. 856), and some reactions of sulfonyl (pp. 921-923) and sulfonyl (p. 907) chlorides result in the formation of disulfides.

Reactions

With Halogens. Diaryl disulfides are converted to sulfonyl halides by the action of chlorine¹⁴⁹ or bromine¹⁵⁰ in anhydrous media.



¹⁴⁵ Otto and Troeger, *Ber.*, **26**, 996 (1893); Price and Twiss, *J. Chem. Soc.* **95**, 1489 (1909); Stutz and Shrmer, *J. Am. Chem. Soc.*, **55**, 1242 (1933).

¹⁴⁶ Zeise, *Ann.*, **11**, 1 (1834); Blanksma, *Rec. trav. chim.*, **20**, 121 (1901).

¹⁴⁷ Binz and Marx, *Ber.*, **40**, 3855 (1907); Bergmann, *Ber.*, **53**, 979 (1920).

¹⁴⁸ Baumann and Fromm, *Ber.*, **28**, 907 (1895).

¹⁴⁹ Warren and Smiles, *J. Chem. Soc.*, 1040 (1932).

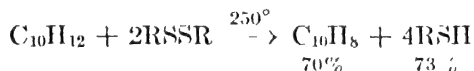
¹⁵⁰ Rheinboldt and Notzkus, *Ber.*, **72**, 657 (1939).

Aliphatic sulfenyl halides have not been obtained by this method (p. 920), apparently because halogenation of the aliphatic groups occurs more readily than cleavage of the disulfide link. In the presence of water both aryl and alkyl disulfides are oxidized by chlorine and bromine to sulfonyl halides (p. 889). Some disulfides form tetrahalides which may be hydrolyzed (p. 907) to thiosulfonic esters.

With Strong Alkali. While disulfides are stable toward dilute alkali, they may be split by strong potassium hydroxide. The initial products ¹⁵¹ are probably mercaptides and sulfenic acids, but the products isolated ¹⁵² are mercaptides and sulfinates (*cf.* p. 921).



Other Reactions. The reductive cleavage of disulfides, which has been discussed (p. 843), is one of their most important reactions. Disulfides may be used for the dehydrogenation of tetralin and other hydroaromatic compounds.¹⁴³



Oxidation (p. 907), reaction with sulfur (p. 865), and formation of sulfonium salts with alkyl halides (p. 867) are other reactions which are discussed elsewhere. Drastic pyrolysis ¹⁵³ of diphenyl disulfide causes disproportionation.



The ease of reduction of disulfides and the ease of their formation from sulfhydryl compounds find an important example in nature in the reversible oxidation-reduction system (like quinone-hydroquinone) cystine-cysteine (p. 1131).

¹⁵¹ Schoberl *et al.*, *Ann.*, **507**, 111 (1933); *Ber.*, **67**, 1545 (1934); *Naturwissenschaften*, **24**, 391 (1935).

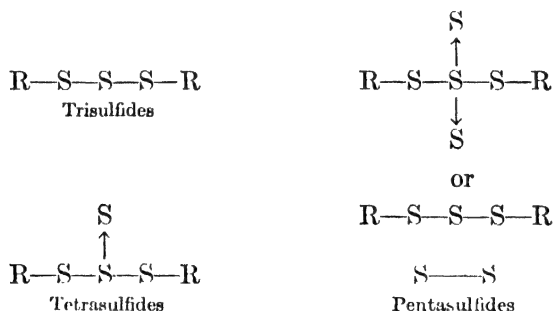
¹⁵² Schiller and Otto, *Ber.*, **9**, 1637 (1876); Pauly and Otto, *Ber.*, **11**, 2070, 2073 (1878); Otto and Rössing, *Ber.*, **20**, 189 (1887); Price and Twiss, *J. Chem. Soc.*, **97**, 1175 (1910); Fromm and Forster, *Ann.*, **394**, 338 (1912); Tocmies and Lavine, *J. Biol. Chem.*, **113**, 571 (1936).

¹⁵³ Hinsberg, *Ber.*, **43**, 1874 (1910).

V. POLYSULFIDES

General Characteristics

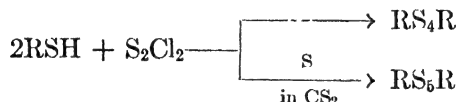
The trisulfides (RS_3R), tetrasulfides (RS_4R), and pentasulfides (RS_5R) have no analogs among oxygen compounds.* Their reactions can be explained by assuming that they are not individual compounds but equilibrium mixtures of disulfides and polysulfides, an assumption which may seem justified by their ease of interconversion. However, parachor¹⁵⁴ and viscosity¹⁵⁵ measurements indicate that trisulfides, tetrasulfides, and pentasulfides are definite compounds and that their structures all contain three sulfur atoms in a linear arrangement.



The polysulfides have not been so completely studied as the other types of sulfur compounds previously discussed. Dimethyl tetrasulfide¹⁵⁶ is said to have a highly repulsive odor.

Preparation

From Sulfhydryl Compounds. The reaction of sulfur chloride (S_2Cl_2) with mercaptans or thiophenols is generally used for the preparation of tetrasulfides^{156, 157}. If the reaction is carried out in the presence of free sulfur¹⁵⁸ in carbon disulfide solution a pentasulfide is obtained.



* The fact that sulfur has a greater tendency to combine with itself than does oxygen is shown by a comparison of the free elements. Whereas oxygen exists as O_2 , or in a metastable form as O_3 , sulfur in solution or in the vapor state is S_8 .

¹⁵⁴ Baroni, *Atti accad. Lincei*, **14**, 28 (1931) [*C. A.*, **26**, 1896 (1932)].

¹⁵⁵ Bezzi, *Gazz. chim. ital.*, **65**, 693 (1935); *ibid.*, **65**, 704 (1935).

¹⁵⁶ Claesson, *J. prakt. Chem.*, [2] **15**, 214 (1877); *Ber.*, **20**, 3413 (1887).

¹⁵⁷ (a) Smythe and Forster, *J. Chem. Soc.*, **97**, 1195 (1910); (b) Tröger and Hornung, *J. prakt. Chem.*, [2] **60**, 113 (1899); (c) Chakravarti, *J. Chem. Soc.*, **123**, 964 (1923); (d) Twiss, *J. Am. Chem. Soc.*, **49**, 491 (1927).

¹⁵⁸ Levi and Baroni, *Atti accad. Lincei*, [6] **9**, 772 (1929) [*C. A.*, **23**, 4927 (1929)].

Thionyl chloride ¹⁵⁹ and sulfuryl chloride ^{159, 160} give several products, including disulfides and trisulfides, when they are allowed to react with sulfhydryl compounds. Tetrasulfides are also produced in reactions in which sulfuryl chloride is used. The reaction ¹⁶¹ of thionyl aniline with *p*-thiocresol gives *p*-tolyltrisulfide and aniline.

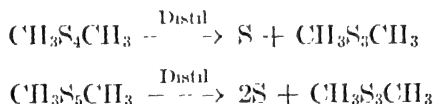
From Organic Sulfides, Disulfides, and Polysulfides. Organic sulfides do not react readily with elementary sulfur. For example, ethyl sulfide is unchanged ¹⁶² after heating with sulfur for four days at 150°. Under more drastic conditions the disulfide and polysulfides are formed.



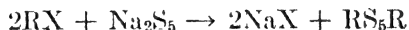
The disulfides, ¹⁶³ in contrast to the sulfides, react readily with sulfur or metal polysulfides and may be converted to trisulfides, ¹⁶⁴ tetrasulfides, ¹⁶⁵ or pentasulfides. ¹⁶⁶ Under similar conditions ¹⁶⁶ trisulfides and tetrasulfides may be converted to pentasulfides. The reaction appears to be catalyzed by ammonia. ¹⁵⁹



Trisulfides may be obtained from tetrasulfides ¹⁵⁶ and pentasulfides ¹⁶⁷ by reversing the above reaction by distillation.



From Sodium Polysulfides. Alkyl sulfates ¹⁶⁷ or alkyl halides ¹⁶⁸ give alkyl polysulfides when allowed to react with sodium or potassium polysulfides. Since the latter are mixtures, the organic products derived from them are also mixtures, but it has been reported that pentasulfides may be obtained by this method. ^{167, 168}



¹⁵⁹ Holmberg, *Ann.*, **359**, 81 (1908).

¹⁶⁰ Tasker and Jones, *J. Chem. Soc.*, **95**, 1910 (1909).

¹⁶¹ Holmberg, *Ber.*, **43**, 226 (1910).

¹⁶² Bottger, *Ann.*, **223**, 348 (1884).

¹⁶³ Claesson, *J. prakt. Chem.*, [2] **15**, 193 (1877); *Bull. soc. chim.*, [2] **25**, 86 (1876).

¹⁶⁴ Muller, *J. prakt. Chem.*, [2] **4**, 39 (1871).

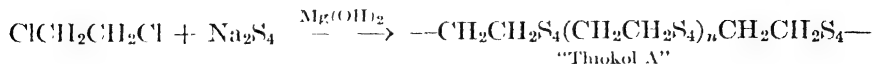
¹⁶⁵ Holmberg, *Ber.*, **43**, 220 (1910).

¹⁶⁶ Levi and Baroni, *Atti accad. Lincei*, **9**, 903 (1929) [*C. A.*, **23**, 5158 (1929)].

¹⁶⁷ Strecker, *Ber.*, **41**, 1105 (1908).

¹⁶⁸ Riding and Thomas, *J. Chem. Soc.*, **123**, 3271 (1923); *ibid.*, **125**, 2214, 2460 (1924).

"Thiokols" are polymeric linear polysulfides prepared by the reaction of dihalides with sodium tetrasulfide. "Thiokol A," for example, is polyethylene tetrasulfide obtained from ethylene chloride and sodium tetrasulfide in the presence of magnesium hydroxide.



The product is obtained in the form of microscopic spherical particles which can be washed by decantation and which will remain for some time as a suspension similar to latex. Coalescence, brought about by acidification, gives a rubbery mass which can be milled, compounded, vulcanized using an accelerator, and in general treated like rubber. The properties of the product may be varied by replacing all or part of the ethylene chloride by β,β' -dichlorodiethyl ether and by decreasing the sulfur content by treating the polymer with sodium sulfide. Though the thiokols resemble natural rubber in appearance and behavior, they do not swell or soften in the presence of hydrocarbon solvents¹⁶⁹ and therefore are used in place of natural rubber when resistance to gasoline or other organic compounds is important.

Other Methods. The reaction¹⁷⁰ of sulfur chloride (S_2Cl_2) with phenylmagnesium bromide gives phenyl sulfide, phenyl disulfide, phenyl trisulfide, phenyl tetrasulfide, chlorobenzene, and diphenyl. Sulfur dioxide and hydrogen chloride produce^{157a} benzyl disulfide and benzyl trisulfide from benzyl mercaptan. Pyrolysis of a disulfide (p. 863) gives a sulfide and a trisulfide.

Reactions

The addition and loss of sulfur, described above, are the most characteristic reactions of polysulfides. Oxidizing agents^{164, 171} produce sulfonic and sulfuric acids from polysulfides. The action of mercury on a trisulfide removes one of the sulfur atoms, producing a disulfide.¹⁶⁴

¹⁶⁹ Patrick, *Trans. Faraday Soc.*, **32**, 347 (1936).

¹⁷⁰ Ferraro and Vinay, *Bull. soc. chim.*, **7**, 518 (1910).

¹⁷¹ Smythe, *J. Chem. Soc.*, **105**, 546 (1914).

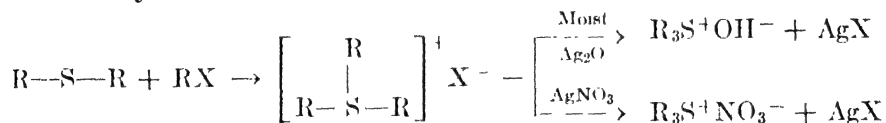
VI. SULFONIUM COMPOUNDS

General Characteristics

The sulfonium compounds * resemble quaternary ammonium compounds in many respects. The tetrahedral configuration of the sulfur atom, with an unshared electron pair at one point of the tetrahedron, is shown by the resolution of unsymmetrical sulfonium salts (p. 419). The salts are crystalline solids which dissolve in water giving neutral solutions. The sulfonium hydroxides are strong bases.

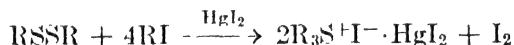
Preparation

From Sulfides. The reaction of alkyl sulfides with alkyl halides occurs slowly at room temperature but more readily upon heating.¹⁷² The reaction is of the second order.¹⁷³ Treatment of the trialkylsulfonium halide with moist silver oxide or with silver nitrate produces the sulfonium hydroxide or nitrate.



Alkyl sulfates, but not alkyl halides,¹⁷⁴ react with alkyl aryl sulfides or with diaryl sulfides to give sulfonium salts.

From Disulfides. The reaction of alkyl halides with disulfides is extremely slow without a catalyst¹⁷⁵ but occurs readily^{175, 176} and gives good yields of sulfonium salts in the presence of such catalysts as mercuric iodide or ferric chloride.



It has been postulated¹⁷⁶ that the initial reaction is the addition of alkyl halide to the disulfide and that the final product is the result of a series of reactions shown below.

* These are known as "sulfoxines" ("Sulfinverbindungen") in the older literature, but this name is misleading since it suggests a resemblance to amines rather than to ammonium compounds.

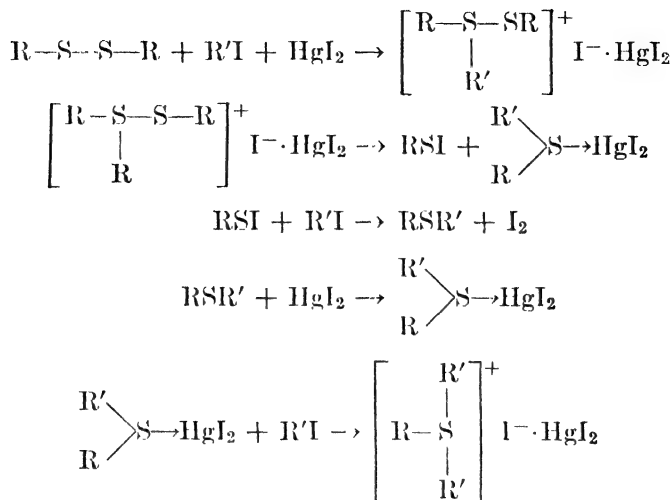
¹⁷² v. Oefele, *Ann.*, **132**, 82 (1864); Cahours, *Ann.*, **135**, 355 (1865).

¹⁷³ Garrara, *Gazz. chim. ital.*, **24**, i, 170 (1894).

¹⁷⁴ (a) Kehrman and Duttonhofer, *Ber.*, **38**, 4197 (1905); *Ber.*, **39**, 3559 (1906); (b) Kehrman and Sava, *Ber.*, **45**, 2895 (1912).

¹⁷⁵ Davies, *Ber.*, **24**, 2548b (1891); Hilditch and Smiles, *J. Chem. Soc.*, **91**, 1394 (1907).

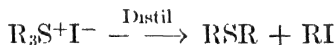
¹⁷⁶ (a) Steinkopf and Müller, *Ber.*, **56**, 1926 (1923); (b) Haas and Dougherty, *J. Am. Chem. Soc.*, **62**, 1004 (1940).



Other Methods. Trialkylsulfonium salts have been prepared by the reaction of an excess of alkyl halide with sulfur¹⁷⁷ or metallic sulfides such as sodium sulfide, cadmium sulfide, or arsenic trisulfide. Aryldialkylsulfonium salts are formed¹⁷⁴ from the reaction of lead mercaptides of thiophenols with alkyl sulfates. Triarylsulfonium salts may be obtained¹⁸⁰ from phenols or their ethers by the action of (1) thionyl chloride in the presence of aluminum chloride, (2) an aromatic sulf-oxide, or (3) a sulfinic acid in the presence of concentrated sulfuric acid. Trimethylsulfonium iodide is formed from the reaction of trithioformaldehyde with methyl iodide in a sealed tube (p. 928).

Reactions of Sulfonium Salts

Pyrolysis. Since the reaction of an alkyl halide with an alkyl sulfide is reversible,¹⁸¹ distillation¹⁴⁹ of a sulfonium salt gives the halide and sulfide.



The reaction occurs readily; this may account for the ease of conversion of unsymmetrical sulfonium salts to mixtures containing the symmetrical salts.¹⁸² For example, trimethylsulfonium iodide and triethylsulfonium iodide are among the products formed by heating¹⁷⁹ methyldiethylsul-

¹⁷⁷ Klinger, *Ber.*, **10**, 1880 (1887), Masson and Kirkland, *J. Chem. Soc.*, **55**, 135 (1889).

¹⁷⁸ Klinger, *Ber.*, **15**, 881 (1882).

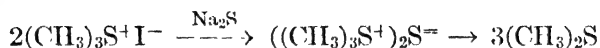
¹⁷⁹ Klinger and Maassen, *Ann.*, **252**, 256 (1889).

¹⁸⁰ Smiles and LeRossignol, *Proc. Chem. Soc.*, **24**, 158 (1906); *J. Chem. Soc.*, **89**, 696 (1906).

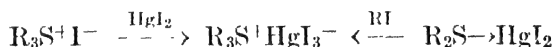
¹⁸¹ Ray and Levine, *J. Org. Chem.*, **2**, 267 (1937).

¹⁸² Meadow and Reid, *J. Am. Chem. Soc.*, **56**, 2177 (1934).

fonium iodide in aqueous solution. Alkyl interchange has also been brought about ¹⁷⁹ by heating a sulfonium salt with alcohol; at 130° triethylsulfonium iodide in methanol gives trimethylsulfonium iodide. Heating sulfonium salts with an excess of sodium sulfide produces dialkyl sulfides; ¹⁸³ this may be due to the disproportionation of the sulfonium sulfides.



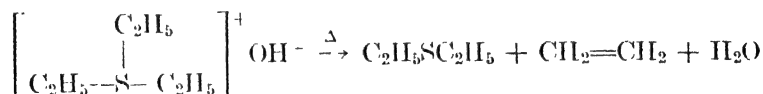
Formation of Addition Compounds. Sulfonium halides form addition products ¹⁸⁴ with salts of the heavy metals such as the halides of copper, mercury, zinc, cadmium, manganese, iron, tin, and platinum. These same products are obtained by the reaction of an alkyl halide with salts formed from sulfides. ^{176b, 185}



Sulfonium compounds are often isolated from reaction mixtures as their addition products with heavy metal salts. Sulfonium salts give crystalline addition products with iodoform. ¹⁸⁶

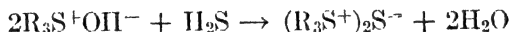
Reactions of Sulfonium Hydroxides

Pyrolysis. The sulfonium hydroxides ^{187, 188} may be isolated from aqueous solutions by evaporation under reduced pressure; they readily decompose, forming an olefin and a sulfide.



This reaction is similar to that obtained by decomposition of quaternary ammonium bases.

Basic Reactions. The sulfonium hydroxides dissolve in water to give solutions which are as basic ¹⁸⁷ as aqueous sodium or potassium hydroxide. Salts are formed by reaction with acids; hydrogen sulfide, for example, produces ^{172, 189} sulfonium sulfides.



¹⁸³ Patein, *Bull. soc. chim.*, [3] **2**, 150 (1889).

¹⁸⁴ Hoffmar and Rabe, *Z. anorg. Chem.*, **14**, 295 (1887); *ibid.*, **17**, 26 (1898); Strömholm, *Ber.*, **31**, 2283, 3285 (1898); *Ber.*, **33**, 823 (1900); *J. prakt. Chem.*, [2] **66**, 423 (1902); Renshaw and Searle, *J. Am. Chem. Soc.*, **55**, 4951 (1933).

¹⁸⁵ Smiles, *J. Chem. Soc.*, **77**, 160 (1900).

¹⁸⁶ Bayer and Co., Ger. pat. 97,207 [*Chem. Zentr.*, **11**, 524 (1898)].

¹⁸⁷ Ostwald, *J. prakt. Chem.*, [2] **33**, 366 (1886).

¹⁸⁸ Alvisi, *Z. anorg. Chem.*, **14**, 302, 308 (1897); Gleave, Hughes, and Ingold, *J. Chem. Soc.*, 236 (1935).

¹⁸⁹ Cahours, *Ann.*, **136**, 151 (1865).

Sulfonium hydroxides¹⁸⁸ liberate ammonia from ammonium salts, form carbonates by reaction with carbon dioxide of the air, and react with metallic aluminum with the liberation of hydrogen.

VII. SULFOXIDES

General Characteristics

The sulfoxides * are odorless, relatively unstable compounds which decompose upon distillation at atmospheric pressure. Diaryl sulfoxides and dialkyl sulfoxides of fairly high molecular weight are solids. The dialkyl sulfoxides of low molecular weight are low-melting solids (e.g.,

O
↑
 $\text{C}_2\text{H}_5\text{SC}_2\text{H}_5$, m.p. $4-6^\circ$); they are soluble in water, alcohol, and ether.

The resolution of unsymmetrical sulfoxides (p. 421) shows the tetrahedral structure of the sulfur atom in these compounds.

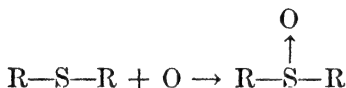
The following discussion will be limited to those compounds in which

O
↑
the —S— group is attached to two carbons. The so-called disulfoxides

O O O
↑ ↑ ↑
(R—S—S—R or R—S—S—R) will be considered later.
↓
O

Preparation

By the Oxidation of Sulfides. The oldest and most common method for the preparation of sulfoxides is the oxidation of sulfides.¹⁹⁰



Probably the best general procedure¹⁹¹ is the addition of the theoretical amount of 30 per cent hydrogen peroxide to a solution of the sulfide in

O
↑
R—S—

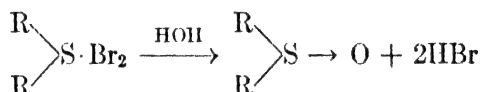
* It should be noted that the R—S— group is known as a sulfinyl group. For example, ethyl sulfoxide may be called ethylsulfinylethane [Patterson, *J. Am. Chem. Soc.*, **55**, 3905 (1933)]. This should not be confused with the convention in the older literature by which the sulfonium compounds are known as sulfines (Sulfinverbindungen) (p. 867).

¹⁹⁰ Saytzeff, *Ann.*, **139**, 354 (1866); *Ann.*, **144**, 148 (1867).

¹⁹¹ (a) Gazdar and Smiles, *J. Chem. Soc.*, **93**, 1834 (1908); (b) Hinsberg, *Ber.*, **43**, 289 (1910).

glacial acetic acid or acetone; the reaction mixture is then allowed to stand at room temperature for one to six days. Other oxidizing agents, such as nitric acid,¹⁹² chromic acid,¹⁹³ hot aqueous potassium permanganate with acetic acid as a solvent for the sulfide,^{192, 194} and perbenzoic acid,¹⁹⁵ may be used.

By Hydrolysis of Dihalides of Sulfides. Many dichlorides and dibromides of sulfides (p. 858) react with water^{113, 196} to give sulfoxides. The hydrolysis may be carried out more readily with dilute alkali or, in the case of sulfide diiodides, with silver acetate.

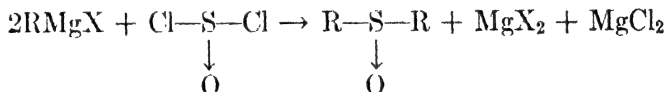


By the Friedel-Crafts Reaction. Diaryl sulfoxides may be obtained¹⁹⁷ by the reaction of aromatic hydrocarbons with thionyl chloride in the presence of aluminum chloride.



It is reported^{197a} that sulfur dioxide may be used in place of thionyl chloride.

From the Grignard Reagent. Sulfoxides are among the products obtained by the reaction of the Grignard reagent with thionyl chloride,^{198, 199} alkyl sulfites,¹⁹⁹ or sulfonyl chlorides.²⁰⁰



¹⁹² Beckmann, *J. prakt. Chem.*, [2] **17**, 441 (1878); Grabowsky, *Ann.*, **175**, 348 (1875)

¹⁹³ Knoll, *J. prakt. Chem.*, **113**, 40 (1926).

¹⁹⁴ Otto, *Ber.*, **13**, 1272 (1880).

¹⁹⁵ Lewin, *J. prakt. Chem.*, **119**, 211 (1928)

¹⁹⁶ Fromm, *Z. angew. Chem.*, **24**, 1125 (1911).

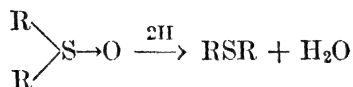
¹⁹⁷ (a) Colby and McLoughlin, *Ber.*, **20**, 195 (1887); (b) Parker, *Ber.*, **23**, 1844 (1890) (c) Smiles and Hilditch, *Proc. Chem. Soc.*, **23**, 161 (1907); (d) Smiles and Bain, *J. Chem. Soc.*, **91**, 1118 (1907); (e) Schönberg, *Ber.*, **56**, 2275 (1923).

¹⁹⁸ Grignard and Zorn, *Compt. rend.*, **150**, 1177 (1910); Bert, *ibid.*, **178**, 1826 (1924).

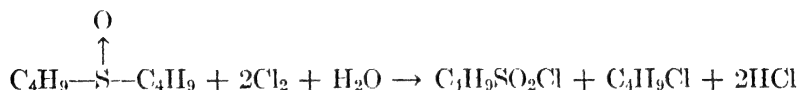
¹⁹⁹ Strecker, *Ber.*, **43**, 1131 (1910).

²⁰⁰ Hepworth and Clapham, *J. Chem. Soc.*, **119**, 1188 (1921).

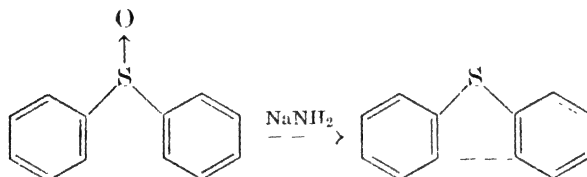
pentachloride,¹⁹² and hydrogen chloride^{203b} (see preceding paragraph) may also produce sulfides.



With Aqueous Chlorine. Chlorination of sulfoxides in the presence of water causes cleavage¹¹⁹ of the sulfur-carbon link, giving sulfonyl chlorides and alkyl chlorides.



Other Reactions. Oxidation of sulfoxides occurs readily, giving sulfones (p. 874). Sulfoxides form addition products with ferric chloride.^{202b} Diphenyl sulfoxide is dehydrated by sodamide, giving dibenzothio-^{197e}phene.



It is of much theoretical interest to know whether the sulfoxide

structure $\begin{pmatrix} \text{O} \\ \uparrow \\ -\text{S}- \end{pmatrix}$ may influence the reactivity of adjacent substituents in the same way as common unsaturated groups influence the reactivity. The full explanation of this question will be given in the discussion of sulfones and the results of the study of sulfoxides will be summarized at that point.

VIII. SULFONES

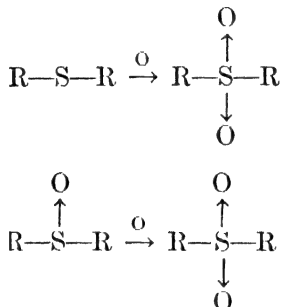
General Characteristics

Monosulfones which contain no other functional group are colorless, odorless, neutral compounds and are usually solids at room temperature (e.g., dimethyl sulfone, m.p. 109°). They are extremely stable both toward chemical reagents and toward pyrolysis; for example, di-*p*-tolyl sulfone (m.p. 158°) boils at 405° without decomposition. The sulfones of low molecular weight are quite soluble in water.

Preparation

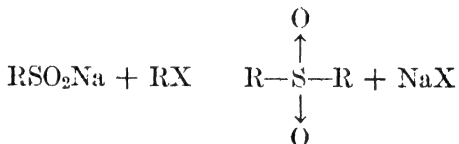
By Oxidation of Sulfides and Sulfoxides. Since the sulfides are readily available and the methods for their oxidation are excellent, they are probably the most general source of sulfones.²⁰⁴ Sulfoxides are also readily oxidized but, since they are also made from sulfides, are seldom used as starting materials in sulfone syntheses.

Hydrogen peroxide^{191b, 205} (30 per cent aqueous solution) is a very satisfactory reagent for the oxidation of sulfides and sulfoxides to sulfones. Acetone or acetic acid are usually employed as solvents, and in some cases^{205b} better yields have been obtained by using a solvent mixture of acetic acid and acetic anhydride. Oxidation is often exothermic and the reaction mixture may require cooling at first; it may then be allowed to stand at room temperature until oxidation is complete.



Potassium permanganate^{51, 206} and chromic acid²⁰⁷ are also satisfactory reagents for the oxidation of sulfides to sulfones, and some oxidations have been carried out using perbenzoic acid.²⁰⁸

By the Action of Alkylating Agents on Salts of Sulfinic Acids. The salts of both aliphatic and aromatic sulfinic acids react with alkylating agents to give sulfones.²⁰⁹



The reaction is limited to alkyl halides, sulfates, etc., and to activated

²⁰⁴ v. Oefele, *Ann.*, **132**, 86 (1864).

²⁰⁵ (a) Pummerer, *Ber.*, **43**, 1407 (1910); (b) Pomerantz and Connor, *J. Am. Chem. Soc.* **61**, 3386 (1939).

²⁰⁶ Bost, Turner, and Norton, *J. Am. Chem. Soc.*, **54**, 1986 (1932).

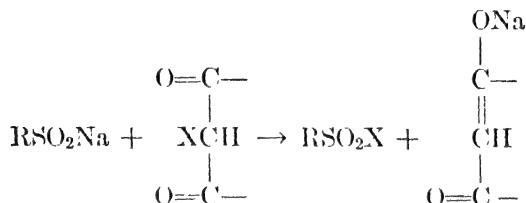
²⁰⁷ Shriner, Struck, and Jorison, *ibid.*, **52**, 2060 (1930).

²⁰⁸ Lewin, *J. prakt. Chem.*, **118**, 282 (1928).

²⁰⁹ Otto, *Ber.*, **13**, 1272 (1880).

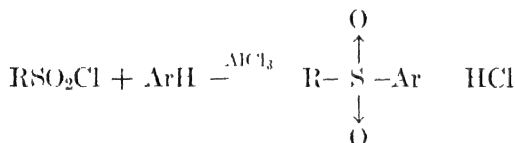
aromatic halides, such as *o*- and *p*-nitrochlorobenzene. Though the reaction is usually satisfactory it should be pointed out that the sulfinates are generally not so reactive in metathesis as are the mercaptides; occasionally the sulfinates are unreactive with halides which will react with mercaptides. Tertiary halides apparently ⁷² do not give sulfones by this method.

Compounds such as ethyl α -chloroacetoacetate, ethyl chloromalonate, diacetylchloromethane, and dibromobarbituric acid which contain "positive" halogen cause oxidation ^{62, 210} of sulfinates, as well as of mercaptides (p. 854).

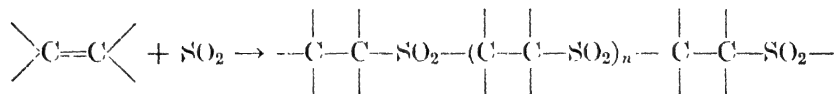


Compounds with two halogens on the same carbon atom do not give disulfones.^{94, 211} Since the initial product of this reaction is an α -halo-sulfone, failure to obtain a disulfone is in agreement with the known behavior of α -bromosulfones (p. 882).

By the Friedel-Crafts Reaction. Diaryl sulfones are obtained by the reaction of sulfonyl chlorides with aromatic compounds in the presence of aluminum chloride.²¹²



By Reactions of Olefins with Sulfur Dioxide. The reaction of mono-olefins with sulfur dioxide gives linear polysulfones, which are described in detail elsewhere (p. 765).

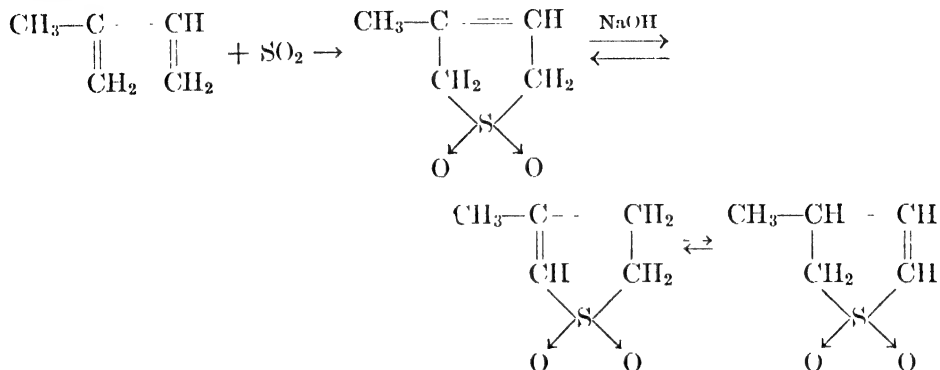


²¹⁰ Otto and Rössing, *Ber.*, **23**, 756 (1890); Kohler and MacDonald, *Am. Chem. J.*, **22**, 227 (1899).

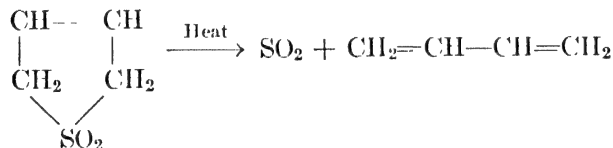
²¹¹ Michael and Palmer, *Am. Chem. J.*, **6**, 253 (1884); Otto and Engelhardt, *Ber.*, **19**, 1835 (1886); Otto, *Ber.*, **21**, 658 (1886).

²¹² Beckurts and Otto, *Ber.*, **11**, 2066 (1878); Olivier, *Rec. trav. chim.*, **33**, 244 (1914), *Chem. Weekblad*, **11**, 372 (1914) [*C. A.*, **10**, 196 (1916)]; Kuczynski, Kuczynski, and Sucharda, *Roczniki Chem.*, **18**, 625 (1938) [*C. A.*, **34**, 3246 (1940)].

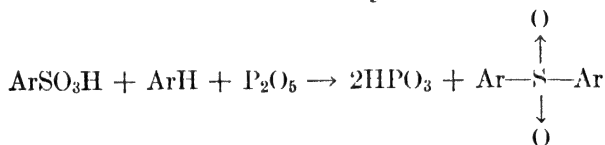
With conjugated diolefins ²¹³ 1,4-addition occurs with the formation of cyclic monomeric sulfones. The addition product from isoprene gives an equilibrium mixture of unsaturated sulfones on treatment with alkali.



The monomeric sulfone from butadiene gives the diene upon heating; this has been applied to the purification of butadiene.²¹⁴



Other Methods. The preparation of sulfones by addition of sulfinic acids to conjugated systems will be discussed later (p. 918). Diaryl sulfones have been obtained ²¹⁵ by the action of phosphorus pentoxide on a mixture of sulfonic acid and aromatic hydrocarbon.



Sulfones are usually by-products of the sulfonation of aromatic hydrocarbons. They appear to be formed ²¹⁶ by the action of S_2O_6 on the hydrocarbon and not, in this case, by condensation of the sulfonic acid with the hydrocarbon. Sulfones have also been obtained by the direct

²¹³ Backer and Strating, *Rec. trav. chim.*, **53**, 525 (1934), *ibid.*, **54**, 170, 618 (1935); Böeseken and van Zuydewijn, *Proc. Acad. Sci. (Amsterdam)*, **40**, 23 (1937) [*C. A.*, **31**, 4953 (1937)]; van Zuydewijn, *Rec. trav. chim.*, **56**, 1047 (1937), Alder, Rickert, and Windemuth, *Ber.*, **71**, 2451 (1938).

²¹⁴ Staudinger and Ritzenthaler, *Ber.*, **68**, 455 (1935); Johnson, Jobling, and Bodamer, *J. Am. Chem. Soc.*, **63**, 133 (1941).

²¹⁵ Michael and Adair, *Ber.*, **10**, 583 (1877); **11**, 116 (1878).

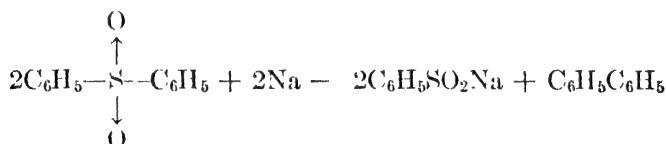
²¹⁶ Michael and Werner, *J. Am. Chem. Soc.*, **58**, 294 (1936).

action of sulfur trioxide²¹⁷ or chlorosulfonic acid²¹⁸ upon aromatic compounds.

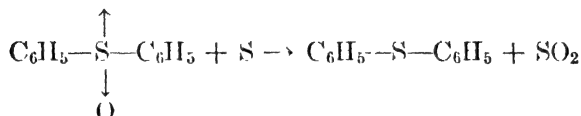
Reactions of Simple Sulfones

This section will be limited to a consideration of the reactions of monosulfones which contain no other functional group. The reactions of disulfones and of substituted sulfones may be considerably different from those of simple monosulfones and will be discussed in another section.

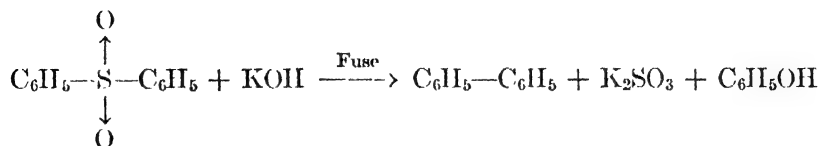
With Reducing Agents. In contrast to the sulfoxides, the sulfones are stable toward most reducing agents. Diphenyl sulfone²¹⁹ is unchanged by treatment with phosphorus at 250° and can be distilled unchanged from zinc dust. Reaction of diphenyl sulfone with sodium²¹⁹ in hot xylene gives biphenyl and sodium benzenesulfinate.



Some sulfones are reduced to sulfides by the action of sulfur, but the reaction is apparently not general.^{219, 220}



With Alkali. The simple sulfones do not react with aqueous alkali under ordinary conditions but are cleaved²²¹ at high temperatures. Diaryl sulfones yield products different from those obtained from dialkyl sulfones (p. 1839). The alkaline fusion of sulfones appears to be a complex reaction giving, in the case of diphenyl sulfone,²²² biphenyl and phenol.



²¹⁷ Zorn and Brunel, *Compt. rend.*, **119**, 1224 (1894).

²¹⁸ Ullmann and Korselt, *Ber.*, **40**, 641 (1907).

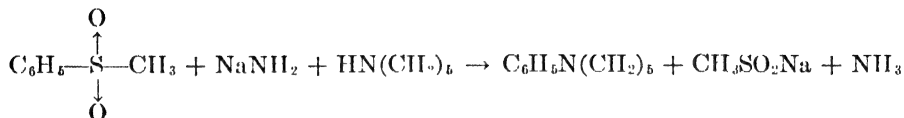
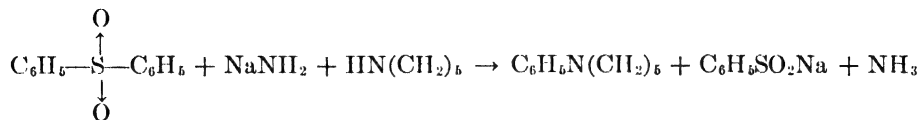
²¹⁹ Krafft and Vorster, *Ber.*, **26**, 2813 (1893).

²²⁰ Böeseken, *Rec. trav. chim.*, **30**, 137 (1911).

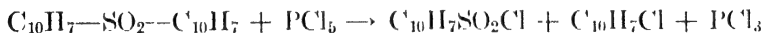
²²¹ Fenton and Ingold, *J. Chem. Soc.*, 2338 (1929).

²²² Otto, *Ber.*, **19**, 2425 (1886).

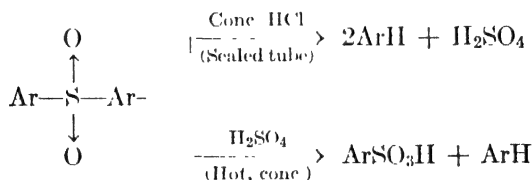
Smooth cleavages of aryl sulfones under mild conditions are accomplished²²³ by treatment with sodamide and piperidine. Dialkyl sulfones are unchanged under these conditions. Diaryl sulfones or alkyl aryl sulfones give N-arylpiperidine and the salt of a sulfonic acid.



Other Reactions. Phosphorus pentachloride usually does not react with sulfones, but dinaphthyl sulfone is converted²²⁴ at high temperatures to the sulfonyl chloride and chloronaphthalene.



Highly methylated diaryl sulfones are hydrolyzed²²⁵ to hydrocarbons by the action of concentrated hydrochloric acid in a sealed tube. Hot concentrated sulfuric acid may give the sulfonic acid.



The reaction of sulfones with the Grignard reagent is discussed later (p. 881).

Certain sulfones give novel rearrangement and sulfonyl interchange reactions which are illustrated below. More complete reviews of this subject may be found elsewhere.²²⁶ Some of these reactions are reversible.²²⁷

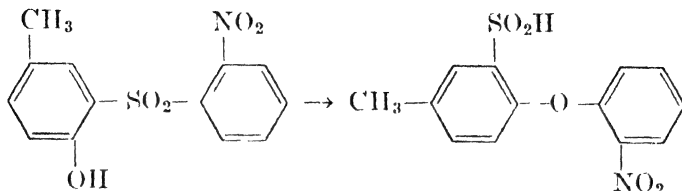
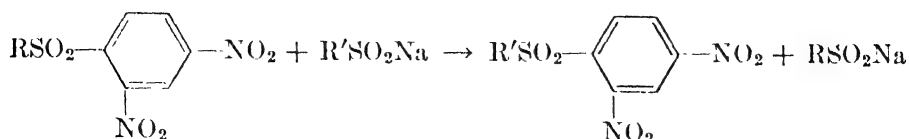
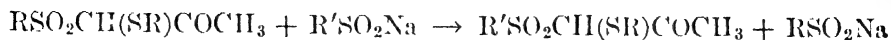
²²³ Bradley, *J. Chem. Soc.*, 458 (1938).

²²⁴ Cleve, *Bull. soc. chim.*, [2] **25**, 256 (1876).

²²⁵ Jacobsen, *Ber.*, **20**, 900 (1887).

²²⁶ *Ann. Reports Chem. Soc. (London)*, **36**, 197 (1939).

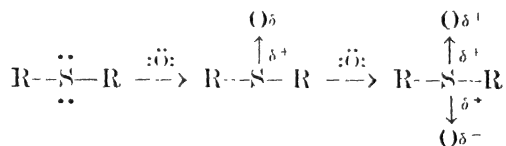
²²⁷ Coats and Gibson, *J. Chem. Soc.*, 442 (1940).



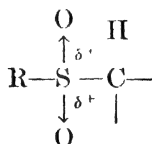
Influence of a Sulfone Group upon Other Atoms and Groups

In the preceding section the reactions which were considered caused alteration of the sulfone function. The following discussion will be devoted to those reactions of sulfones which are due to the influence of the sulfone group upon the rest of the molecule. The reactions of simple sulfones which may be attributed to activation of hydrogen by the sulfone group will be included, but all other cases will involve substituted sulfones, including polysulfones.

Influence upon Hydrogen. In considering the oxidation of a sulfide to a sulfoxide or a sulfone, it would seem that acquisition by a neutral oxygen atom of a share in two electrons from sulfur would result in a fractional negative charge on oxygen and a corresponding positive charge * on sulfur. That is, sulfur becomes the positive end of the dipole.



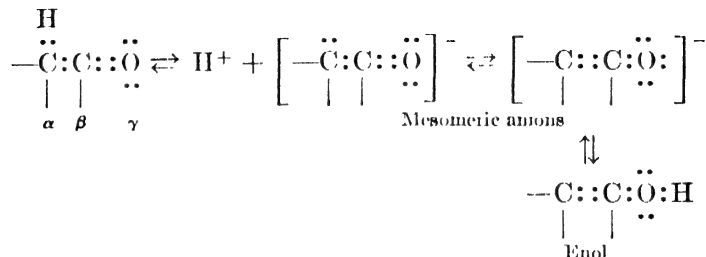
As a result the sulfur should exert a considerable electron attraction and facilitate removal of a proton from an adjacent carbon.



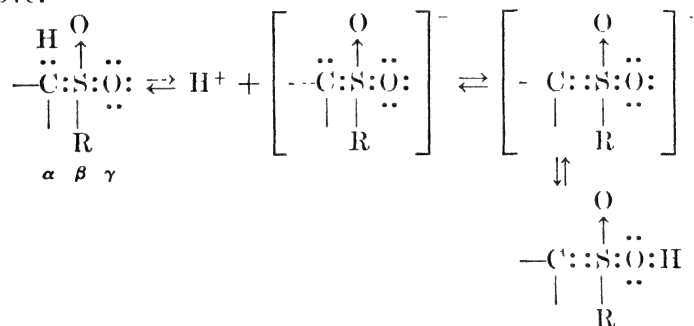
As explained elsewhere (Chapter 25), an effective group for prototropic

* The symbols δ^- and δ^+ are used here, in conformity with Chapter 25, to distinguish fractional charges from integral (+ and -) charges.

change not only must have a strong electron attraction but also must provide a suitable seat for the charge on the anion. The enolization of a carbonyl compound is an example of prototropy in a system fulfilling both these requirements.



The corresponding β - and γ -atoms in sulfones are connected by a single pair of electrons, and the anions are therefore different from those pictured above.



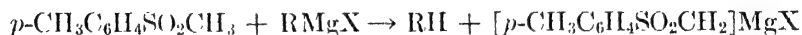
One of the formulas of the anions has an unshared electron pair on carbon, and the other requires that sulfur expand its valence shell to ten electrons.* It will be shown below that anions derived from the sulfones may be formed. These will be represented by noncommittal formulas since it appears that neither of the alternative electronic formulas is universally accepted. Regardless of the opinion concerning this structure it must be conceded that the sulfone group is an electron-attracting (+I) group† with less tendency than other such labilizing groups (>C=O , $\text{--C}\equiv\text{N}$, --NO_2 , etc.) to undergo polarization† (*E* effect, p. 1847).

* For a more detailed discussion see Shriner, Struck, and Jorison, *J. Am. Chem. Soc.*, **52**, 2060 (1930); Gibson, *Chem. Rev.*, **14**, 431 (1934); Arndt and Martius, *Ann.*, **499**, 228 (1932).

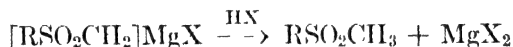
† In other words the sulfone group increases the acidity because it facilitates the removal of a proton but it has no great tendency to participate in enolization. The justification of this viewpoint is discussed by Arndt and Martius (*loc. cit.*). A concise summary is given in *Ann. Repts. Chem. Soc. (London)*, **31**, 193 (1934). The terms *I* and *E* effects are used in the same sense as in Chapter 25.

From the above consideration it may be said that differences between the sulfone group and the other labilizing groups in their activation of hydrogen in the α -position will be due to the following: (1) the high electron attraction of the sulfone group; (2) the failure of the sulfone group to provide a suitable seat for the charge on the anion; (3) the necessity in many cases for the sulfones to react by different reaction mechanisms. This third difference arises from the fact that the sulfone group does not contain a normal covalent double bond; therefore, reactions involving preliminary addition to an unsaturated function would require, in this case, expansion of the valence shell of sulfur. Though this possibility cannot be rejected²²⁸ the tendency for the sulfone to react in this way would at least be considerably different from the tendency of an unsaturated group (e.g., carbonyl) to undergo addition. Therefore, a comparison of the behavior of sulfones with that of compounds containing unsaturated labilizing groups should reveal the properties due to electron attraction with complicating factors (enolization, addition, etc.) minimized.

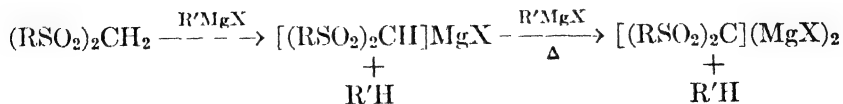
Activation of hydrogen in the α -position by the sulfone group is shown by the reaction of sulfones with the Grignard reagent,^{90, 94, 229} liberating a hydrocarbon and forming a halomagnesium derivative of a sulfone.



The halomagnesium derivatives behave like enolates in their reactions; they may be acylated, alkylated, or halogenated and upon hydrolysis regenerate the sulfone.



In some cases sulfones do not react with the Grignard reagent at room temperature; temperatures of 75–80° will bring about reaction. When two sulfone groups are attached to the same carbon (methylene disulfones, $\text{RSO}_2\text{CH}_2\text{SO}_2\text{R}$) the acidity of the hydrogen is more pronounced; these compounds react with the Grignard reagent at room temperature and at high temperatures react with two moles of the reagent.



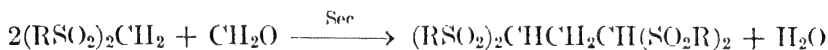
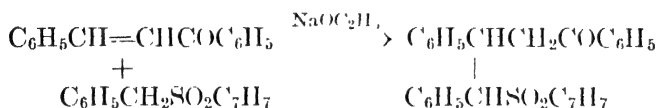
²²⁸ Sidgwick, "The Electronic Theory of Valency," Oxford University Press, London (1929), p. 152. Recent experiments suggest that in certain sulfides the sulfur may expand its valence shell, and thus cause activation of the methylene group: Rothstein, *J. Chem. Soc.*, 1550, 1553, 1558, 1560 (1940).

²²⁹ (a) Kohler and Tishler, *J. Am. Chem. Soc.*, **57**, 218 (1935); (b) Kohler and Potter *ibid.*, **57**, 1316 (1935); (c) Kohler and Larson, *ibid.*, **57**, 1448 (1935).

The reaction of the Grignard reagent with sulfones is analogous to that with ketones in which steric hindrance prevents addition to the carbonyl group (p. 646).

While in simple sulfones the hydrogen is not sufficiently activated to form sodium salts readily, methylene disulfones react with sodium ethoxide ²⁰⁷ and in some cases ²⁵ with dilute aqueous alkali to form sodium derivatives. Trisulfonylmethanes, $(\text{RSO}_2)_3\text{CH}$, are still more acidic.²³⁰ Methylene disulfones behave like enolizable compounds in the reaction ²³¹ with mercuric chloride-sodium ethoxide.

A few cases are known in which sulfones undergo reactions that are considered typical of compounds containing hydrogen activated by unsaturated groups (such as carbonyl). Methyl *p*-tolyl sulfone reacts ^{229b} with benzaldehyde to give low yields of an unsaturated sulfone, a reaction analogous to the formation of benzalacetophenone from acetophenone and benzaldehyde. Benzyl *p*-tolyl sulfone undergoes the Michael condensation,²³¹ and the reaction ²³² of a disulfone with formaldehyde in the presence of a secondary amine is analogous to the Knoevenagel reaction.



These reactions and the alkylation ^{207, 229, 233} of metallic derivatives of disulfones are indications that activation of hydrogen by the sulfone group is similar to that by the ketone and other unsaturated groups. These results can be explained either by assuming that sulfur may expand its valence shell or that enolization is unnecessary for these reactions. The failure ^{231, 234} of other active methylene reactions to occur with sulfones may be attributed to (1) the lesser activating power of the sulfone group, (2) the necessity of an enolic intermediate, or (3) a reaction mechanism requiring addition to an unsaturated group.

Influence upon Halogen. The sulfone group causes α -halogen to be inactive as far as metathesis reactions are concerned,^{93b, 235} suggesting

²³⁰ Cowie and Gibson, *J. Chem. Soc.*, 306 (1933).

²³¹ Connor, Fleming, and Clayton, *J. Am. Chem. Soc.*, **58**, 1386 (1936).

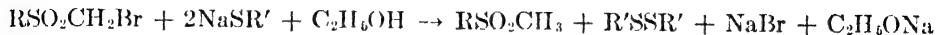
²³² Kotz, *Ber.*, **33**, 1123 (1900).

²³³ Shriner and Greenlee, *J. Org. Chem.*, **4**, 242 (1939).

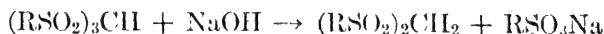
²³⁴ Barnes, Kundinger, and McElvain, *J. Am. Chem. Soc.*, **62**, 1282 (1940).

²³⁵ Michael and Palmer, *Am. Chem. J.*, **6**, 253 (1884).

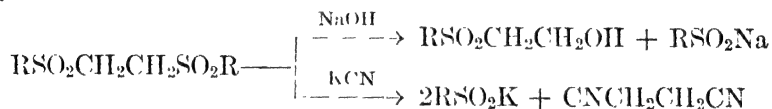
that the increased reactivity usually associated with α -halo esters, ketones, etc., is a result of a preliminary addition reaction. The sulfone group activates α -halogen^{93b, 94, 229a, 233-236} in respect to oxidation reactions ("positive" halogen).



Influence upon Sulfone Groups. In general, the disulfones and polysulfones are less stable than the simple sulfones. Disulfonylmethanes* are not hydrolyzed by alkali, but trisulfonylmethanes^{232, 237} are cleaved to disulfones and sulfonates.

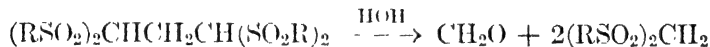


When sulfone groups are attached to adjacent carbon atoms, cleavage occurs more readily than when the groups are on the same atom (Stuffer's rule²³⁸). The cleavage reactions of ethylene disulfones produce sulfonates.^{94, 237-239}



The alkaline hydrolysis of ethylene disulfones has been applied in studies of the structures of the linear polysulfones from sulfur dioxide and olefins (p. 766).

Trimethylene disulfones²⁴⁰ are not hydrolyzed by alkali, but a tetrasulfonyl propane is reported²³² to give formaldehyde and the disulfone.



α -Disulfones²⁴¹ may be prepared by oxidation of sulfinic acids, by re-

²³⁶ Mellander, *Arkiv Kemi, Mineral. Geol.*, **12A**, No. 16, 32 (1937) [*C. A.*, **31**, 5763 (1937)]; Savinen, *Arkiv Kemi, Mineral. Geol.*, **12B**, No. 51 (1938) [*C. A.*, **32**, 4520 (1938)].

* Sulfonal $(\text{CH}_3)_2\text{C}(\text{SO}_2\text{C}_2\text{H}_5)_2$, trional $\text{C}_2\text{H}_5\text{C}(\text{CH}_3)(\text{SO}_2\text{C}_2\text{H}_5)_2$, and tetronal $\text{C}_2\text{H}_5)_2\text{C}(\text{SO}_2\text{C}_2\text{H}_5)_2$ are used as soponics. They are prepared by oxidation of the appropriate mercaptols or by alkylation of a disulfone obtained from a mercaptal. [Baumann, *Ber.*, **19**, 2898 (1888); Baumann and Kast, *Z. physiol. Chem.*, **14**, 52 (1889)].

²³⁷ Hohnberg, *Ber.*, **40**, 1740 (1907); Baumann and Walter, *Ber.*, **26**, 1124 (1893); Baumann, *Ber.*, **24**, 2272 (1891); Otto, *Ber.*, **24**, 1832 (1891).

²³⁸ Stuffer, *Ber.*, **23**, 1408, 3226 (1890).

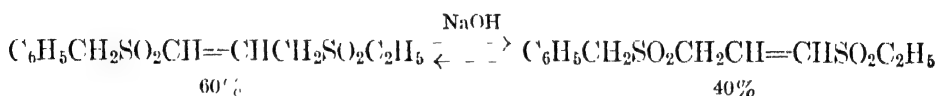
²³⁹ Otto and Damkohler, *J. prakt. Chem.*, [2] **30**, 171 (1884); Otto, *ibid.*, **30**, 361 (1884).

²⁴⁰ Autenrieth and Wolff, *Ber.*, **32**, 1368 (1899).

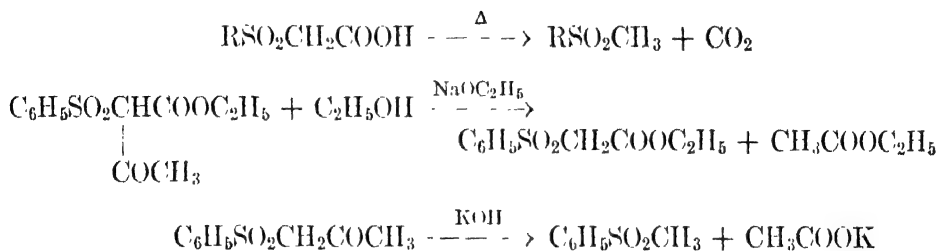
²⁴¹ Hilditch, *J. Chem. Soc.*, **93**, 1524 (1908); Himsberg, *Ber.*, **49**, 2593 (1916); Kohler and MacDonald, *Am. Chem. J.*, **22**, 219 (1899); Pearl, Evans, and Dehn, *J. Am. Chem. Soc.*, **60**, 2478 (1938).

system has some bearing on the theoretical considerations (expansion of valence shell, etc.) already discussed. For example, the products obtained from the reactions of α,β -unsaturated sulfones with the Grignard reagent behave²²⁹ like those obtained from the reaction of α,β -unsaturated ketones. This suggests²²⁹ that the reactions of the sulfones, like those of the ketones, occur by 1,4-addition with expansion of the valence shell of sulfur.

In unsaturated sulfones with a methylene group between the double bond and the sulfone group, tautomerism may occur^{213, 244} in the three-carbon system.



α -Sulfonyl Ketones, Acids, etc. The α -sulfonyl acids may be isolated but are readily decarboxylated by heat.²⁴⁵ The sulfonyl group is apparently effective^{93, 210, 246} in causing the hydrolysis or alcoholysis of keto and other groups.



Comparison of Activating Effects of Sulfone and Sulfoxide Groups

The important difference²⁰⁷ in the electronic structures of sulfones and sulfoxides is that the sulfoxides have only one coördinate link and hence retain an unshared electron pair. The sulfoxide group, therefore, does not have a strong attraction for electrons²⁴⁷ and does not activate hydrogen in the α -position.²⁰⁷

²⁴⁴ Rothstein, *J. Chem. Soc.*, 684 (1934); *ibid.*, 309 (1937).

²⁴⁵ Otto, *Ber.*, **21**, 89, 992 (1888).

²⁴⁶ Otto and Otto, *J. prakt. Chem.*, [2] **36**, 401 (1887); Otto and Rössing, *Ber.* **23** 752 (1890).

²⁴⁷ Hammick and Williams, *J. Chem. Soc.*, 211 (1938).

IX. SULFONIC ACIDS AND THEIR DERIVATIVES

General Characteristics

Many aliphatic sulfonic acids * are highly hygroscopic. Those of low molecular weight are high-boiling liquids (e.g., $\text{CH}_3\text{SO}_3\text{H}$, b.p. 167° [10 mm.]), but the higher members of the series are crystalline solids. Since $-\text{SO}_3\text{H}$ is a polar, water-solubilizing group, the aliphatic sulfonic acids which contain a long hydrocarbon chain are detergents ("hydrogen soaps"). Their sodium salts † are excellent detergents and may be used in hard water since the calcium and magnesium salts are very soluble.

The aromatic sulfonic acids are useful intermediates in synthesis because the $-\text{SO}_3\text{H}$ group is readily replaced by other substituents. Many dyes contain this group because of its water-solubilizing action.

Some of the aliphatic sulfonamides of low molecular weight are hygroscopic, but generally sulfonamides are crystalline solids which are well suited as derivatives for the identification of sulfonic acids or of amines. Aliphatic sulfonyl chlorides are lachrymatory liquids, but the aromatic sulfonyl chlorides are, with a few exceptions, solids. The esters

of sulfonic acids $\left[\begin{array}{c} \text{O} \\ \uparrow \\ \text{R}-\text{S}-\text{OR} \\ \downarrow \\ \text{O} \end{array} \right]$ are isomeric with alkyl sulfites $\left(\begin{array}{c} \text{O} \\ \uparrow \\ (\text{ROSOR}) \end{array} \right)$

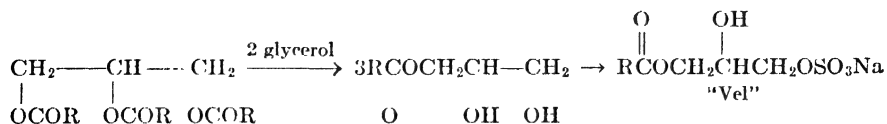
but the two series differ considerably in chemical and physical properties.

* The approved convention [Patterson, *J. Am. Chem. Soc.*, **55**, 3915, 3920 (1933)] is to name sulfonic acids and their derivatives as derived from hydrocarbons. However, in the nomenclature of sulfones the acyl radicals derived from sulfonic acids are alkylsulfonyl radicals. For example: $\text{CH}_3\text{SO}_3\text{H}$, methanesulfonic acid; $\text{CH}_3\text{SO}_2\text{Cl}$, methanesulfonyl chloride; $\text{C}_6\text{H}_5\text{SO}_2\text{OC}_2\text{H}_5$, ethyl benzenesulfonate; $\text{CH}_3\text{SO}_2\text{CH}_2\text{COOH}$, methylsulfonyl acetic acid; $\text{C}_6\text{H}_5\text{SO}_2\text{CH}_2\text{COOH}$, phenylsulfonyl acetic acid.

† These are not to be confused with the commoner "soapless detergents," which are sodium alkyl sulfates, not sulfonates. Some of the sulfates are prepared by neutralizing the alkyl acid sulfates which are formed by the action of concentrated sulfonic acid upon a mixture of high-molecular-weight alcohols (average, about C_{12}) obtained by the hydrogenation of glycerides.



These products are sold in "Dreft" and "Drene." "Vel" is likewise a sulfate.



Preparation

By Sulfonation. Alkanesulfonic acids are formed in low yields (less than 40 per cent) by the action of fuming sulfuric acid ²⁴⁸ or chlorosulfonic acid ²⁴⁹ upon paraffin hydrocarbons.



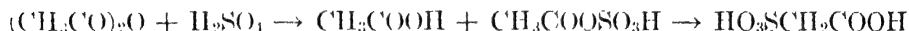
The reaction occurs more readily with branched-chain hydrocarbons than with normal hydrocarbons. Some disulfonic acids are obtained ²⁴⁸ by passing sulfur trioxide through boiling paraffin.

Sulfonation of aliphatic hydrocarbons may be carried out with sulfonyl chloride ²⁵⁰ provided that pyridine, quinoline, or a sulfhydryl compound is added to suppress the chlorination reaction. The reaction mixture is irradiated during sulfonation. In this way a 55 per cent yield of cyclohexanesulfonyl chloride may be obtained.

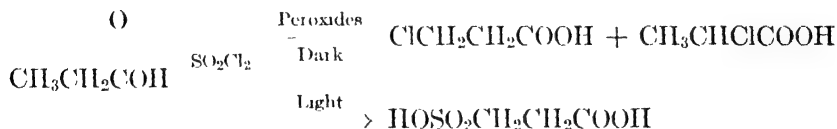
The sulfonation of olefins is described elsewhere (p. 177).

Sulfonic acids are formed by sulfonation during the refining of petroleum distillates, and their salts are used as detergents, emulsifying agents, wetting agents, cutting oil, etc.

Carboxylic acids and anhydrides are more readily sulfonated than the hydrocarbons. Aliphatic carboxylic acids have been converted to α -sulfo acids by reaction with sulfuric acid,²⁵¹ sulfur trioxide,²⁵² and chlorosulfonic acid.²⁵³ Kinetic studies ²⁵⁴ indicate the following mechanism for the sulfonation of acetic anhydride.



Aliphatic acids react with sulfonyl chloride in an unusual manner ²⁵⁵ giving sulfonation in the β -position. This reaction is favored by light and by the absence of peroxides. Peroxides catalyze the chlorination reaction, which occurs in the α -, β -, and γ -positions.



²⁴⁸ Worstall, *Am. Chem. J.*, **20**, 664 (1898).

²⁴⁹ Young, *J. Chem. Soc.*, **75**, 172 (1899).

²⁵⁰ Kharasch and Read, *J. Am. Chem. Soc.*, **61**, 3089 (1939).

²⁵¹ Franchimout, *Compt. rend.*, **92**, 1054 (1881); *Rec. trav. chim.*, **7**, 27 (1888).

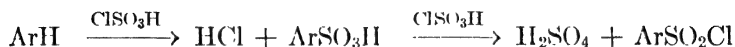
²⁵² Melsens, *Ann.*, **52**, 276 (1884).

²⁵³ Baumstark, *Ann.*, **140**, 81 (1866).

²⁵⁴ Murray and Kenyon, *J. Am. Chem. Soc.*, **62**, 1230 (1940).

²⁵⁵ Kharasch and Brown, *ibid.*, **62**, 925 (1940).

The sulfonation of aromatic hydrocarbons is the common method of preparation of aromatic sulfonic acids and is too familiar to warrant a detailed discussion. The mechanism of this reaction has been discussed elsewhere (p. 175). Fuming sulfuric acid or chlorosulfonic acid are the sulfonating agents used. Chlorosulfonic acid appears to form the sulfonic acid first ²⁵⁶ but an excess of it produces the sulfonyl chloride.



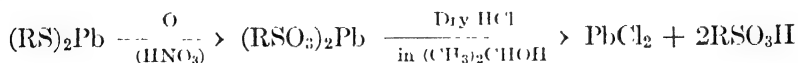
Mercuric sulfate ²⁵⁷ and silver sulfate are catalysts for sulfonation.

The temperature of sulfonation may have an important influence upon the ratio of isomers produced. For example, sulfonation of toluene at low temperatures gives a relatively large amount of the *ortho* isomer. *o*-Toluenesulfonic acid and *p*-toluenesulfonic acid are interconvertible on heating with concentrated sulfuric acid. The reaction is considered ²⁵⁸ to be intramolecular. High temperatures (200–250°) are necessary for the formation of disulfonic acids. Disulfonation of benzene gives predominantly the *meta* isomer with a small amount of the *para* derivative; high temperatures and the presence of moisture accelerate the formation of an equilibrium mixture ²⁵⁹ of the two. Introduction of a third sulfonic acid group is usually brought about at a higher temperature obtainable with a sulfuric acid-potassium bisulfate mixture.

Sulfonation of polymethyl benzenes or methylhalobenzenes ²⁶¹ may give rearrangements. For example, durene gives pentamethylbenzene and a mixture of two trimethylbenzenesulfonic acids.

Sulfonation has been suggested ²⁶² as a method for the identification of aryl halides and ethers.

By Oxidation of Sulfhydryl Compounds. The oxidation of lead mercaptides by nitric acid ²⁶³ is an excellent method for the preparation of aliphatic sulfonic acids. The lead sulfonates obtained by this method are readily converted to sulfonic acids by treatment with dry hydrogen chloride in isopropyl alcohol. The yields are 60–92 per cent.



²⁵⁶ Harding, *J. Chem. Soc.*, **119**, 1261 (1921); Stewart, *ibid.*, **121**, 2556 (1922).

²⁵⁷ Behrend and Mertelsmann, *Ann.*, **378**, 352 (1911); Holdermann, *Ber.*, **39**, 1250 (1906).

²⁵⁸ Hollemann and Caland, *Ber.*, **44**, 2504 (1911).

²⁵⁹ Polak, *Rec. trav. chim.*, **14**, 416 (1910).

²⁶⁰ Smith and Cass, *J. Am. Chem. Soc.*, **54**, 1614 (1932); Jacobsen, *Ber.*, **19**, 1209 (1886).

²⁶¹ Jacobsen, *Ber.*, **20**, 2837 (1887); Tohl, *Ber.*, **25**, 1523 (1892).

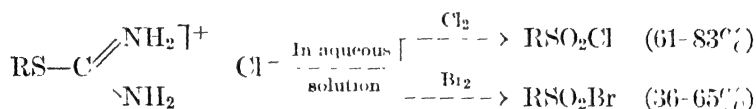
²⁶² Huntress and Carton, *J. Am. Chem. Soc.*, **62**, 511 (1940).

²⁶³ Noller and Gordon, *ibid.*, **55**, 1093 (1933); Vivian and Reid, *ibid.*, **57**, 2559 (1935).

Other oxidizing agents which have been used for the oxidation of mercaptans to sulfonic acids are potassium permanganate²⁶⁴ and hydrogen peroxide.²⁶⁵ The action of chlorine or bromine in acetic acid or in water converts^{266, 267} mercaptans and thiophenols to sulfonyl chlorides or sulfonyl bromides.



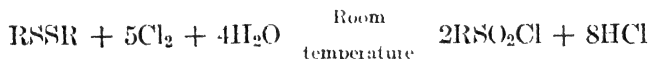
By Oxidation of Other Compounds. The preparation of alkanesulfonyl halides has been carried out with excellent results by the oxidation^{13, 268} of S-alkylisothiuronium salts (p. 841) with aqueous halogen. This process is superior to the one mentioned above because it avoids the isolation of the mercaptans.



The chief objection to this method is that a few serious explosions have occurred.²⁶⁹ In these cases it appears that the reaction product was not isolated immediately after the introduction of the amount of chlorine necessary for the formation of sulfonyl chloride and that nitrogen trichloride may have been formed.

The formation of sulfonyl halides or sulfonic acids has been reported^{13, 267-270} by the application of this reaction to thioesters, S-alkylthiourethanes, thiolsulfonic esters, thiocyanates, alkylmercaptopyrimidines, S-alkyltrimethylisothiourcas, xanthates, and similar compounds.

Although the starting materials are somewhat less conveniently prepared, the chlorination of disulfides¹¹⁹ seems to offer a method of synthesis of sulfonyl chlorides without any possibility of the formation of nitrogen chlorides. The disulfide is dissolved in glacial acetic acid, the theoretical amount of water added, and chlorine passed in. The reaction is complete in a few minutes.



²⁶⁴ Autenrieth, *Ann.*, **259**, 363 (1890); Collins, Hilditch, Marsh, and McLeod, *J. Soc. Chem. Ind.*, **52**, 272T (1933).

²⁶⁵ Baeker, *Rec. trav. chim.*, **54**, 205 (1935).

²⁶⁶ Zincke and Frohneberg, *Ber.*, **43**, 837 (1910); Young, *J. Am. Chem. Soc.*, **59**, 811 (1937).

²⁶⁷ Douglass and Johnson, *J. Am. Chem. Soc.*, **60**, 1486 (1938).

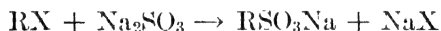
²⁶⁸ Sprague and Johnson, *ibid.*, **59**, 1837, 2439 (1937).

²⁶⁹ Folkers, Russell, and Bost, *ibid.*, **63**, 3530 (1941).

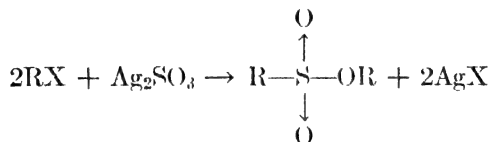
²⁷⁰ Battegay and Krebs, *Compt. rend.*, **206**, 1262 (1938); Johnson and Douglass, *J. Am. Chem. Soc.*, **61**, 2549 (1939); Johnson, *Proc. Natl. Acad. Sci. U. S.*, **25**, 448 (1939) [*C. A.*, **34**, 2811 (1940)]; Stone, *J. Am. Chem. Soc.*, **62**, 571 (1940).

Diaryl disulfides ²⁷¹ may require more vigorous conditions for oxidation. Mercaptals, mercaptols, and sulfoxides, which also give sulfonyl chlorides ¹¹⁹ under these conditions, are not readily enough available to appear as promising materials for use of this reaction in synthesis (pp. 858, 873). Trithioformaldehyde, however, is a good source ¹¹⁹ of chloromethanesulfonyl chloride (p. 858).

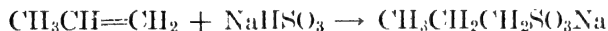
By the Strecker Reaction. Alkyl halides react ²⁷² with sodium or ammonium sulfite to give salts of alkanesulfonic acids. Alkyl bromides are generally used, but it is claimed ²⁷³ that better yields (90–99 per cent) may be obtained by using alkyl chlorides in an autoclave at 200°. The sulfonic acids may be isolated ²⁷⁴ as their barium salts, liberated with sulfuric acid, and converted to phenylhydrazonium salts. The Strecker reaction may be applied to polymethylene halides ²⁷⁵ or branched-chain halides. ²⁷⁶



Silver sulfite reacts ²⁷⁷ with alkyl iodides to give esters of sulfonic acids.



By Addition of Bisulfites to Olefins. ⁶⁸ Olefins apparently do not react with bisulfites in the absence of oxygen. In the presence of oxygen addition occurs ²⁷⁸ in a manner opposite to that predicted by Markownikoff's rule ("abnormal addition"). Yields vary from 12 per cent (ethylene) to 90 per cent (cinnamyl alcohol).



Three sulfonic acids have been obtained ²⁷⁹ from the reaction of styrene with ammonium bisulfite in the presence of oxygen.

²⁷¹ Schreiber and Shriner, *J. Am. Chem. Soc.*, **56**, 114 (1934).

²⁷² Strecker, *Ann.*, **148**, 90 (1868); Reed and Tartar, *J. Am. Chem. Soc.*, **57**, 570 (1935).

²⁷³ Turkiewicz and St. Pilat, *Ber.*, **71**, 284 (1938).

²⁷⁴ Latimer and Bost, *J. Am. Chem. Soc.*, **59**, 2500 (1937); *J. Org. Chem.*, **5**, 24 (1940).

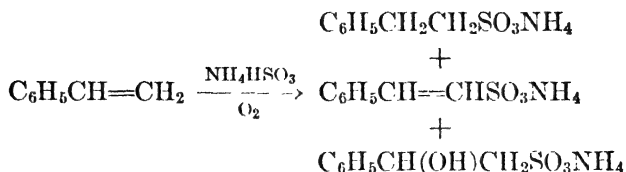
²⁷⁵ Stone, *J. Am. Chem. Soc.*, **58**, 488 (1936). See also Stone, Ref. 270.

²⁷⁶ Zuffanti, *J. Am. Chem. Soc.*, **62**, 1044 (1940).

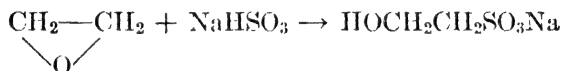
²⁷⁷ Kurbatow, *Ann.*, **173**, 7 (1874). Alkyl sulfites are also obtained by the action of thionyl chloride on alcohols. Voss and Wachs, *Ber.*, **68**, 1939 (1935). See also Ref. 281.

²⁷⁸ Kharasch, May, and Mayo, *Chem. and Ind.*, **16**, 774 (1938); *J. Org. Chem.*, **3**, 175 (1938); Kolker and Lapworth, *J. Chem. Soc.*, **127**, 307 (1925).

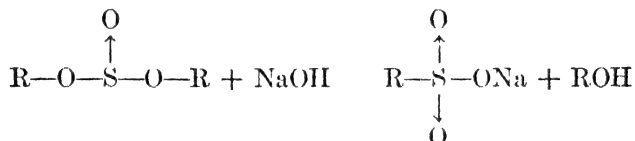
²⁷⁹ Kharasch, Schenck, and Mayo, *J. Am. Chem. Soc.*, **61**, 3092 (1939).



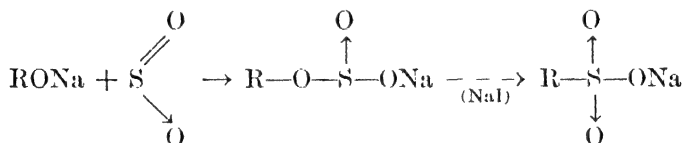
Other Methods. The formation of salts of α -hydroxy sulfonic acids (aldehyde and ketone bisulfites) and of sulfonates by addition to α,β -unsaturated ketones, etc., is discussed elsewhere (p. 677). β -Hydroxy-sulfonates may be obtained²⁸⁰ by the reaction of alkylene oxides with sodium bisulfite.



Alkaline hydrolysis of alkyl sulfites²⁷⁷ causes rearrangement from oxygen to sulfur and gives sulfonic acids.²⁴



Sodium alkyl sulfites, obtained by the reaction of alkoxides with sulfur dioxide, undergo a similar reaction²⁸¹ in the presence of salts such as sodium iodide.



Formation of Acid Derivatives. The conversion of sulfonic acids and their salts to sulfonyl chlorides may be carried out by the use of chlorosulfonic acid,²⁸⁶ phosphorus pentachloride,²⁸² benzotrichloride,²⁸³ or an excess of thionyl chloride.²⁸⁴ The use of acid chlorides for the synthesis of esters and amides will be described with the other reactions of sulfonyl chlorides. Sulfonyl iodides are prepared from salts of sulfinic acids (p. 917). Sulfonic anhydrides, $(\text{RSO}_2)_2\text{O}$, are known²⁸⁵ but are not important.

²⁸⁰ Lauer and Hill, *J. Am. Chem. Soc.*, **53**, 1873 (1936).

²⁸¹ Rosenheim and Sarow, *Ber.*, **38**, 1303 (1905); Rosenheim and Liebknecht, *Ber.*, **31**, 405 (1898).

²⁸² Joy and Bogert, *J. Org. Chem.*, **1**, 236 (1936).

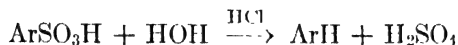
²⁸³ Ger. pat. 574,836 [*C. A.*, **27**, 4543 (1933)].

²⁸⁴ Sutherland and Shriner, *J. Am. Chem. Soc.*, **58**, 63 (1936); Smiles and Hilditch, *J. Chem. Soc.*, **91**, 522 (1907).

²⁸⁵ Hubner, *Ann.*, **223**, 238 (1884); Abrahall, *J. Chem. Soc.*, **49**, 692 (1886); Rosenberg *Ber.*, **19**, 652 (1886); Armstrong, *Ber.*, **25C**, 752 (1892).

Reactions Resulting in Replacement of the Sulfonate Group

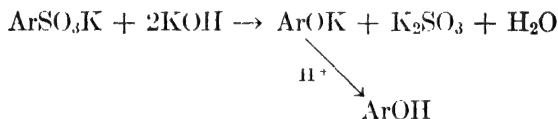
Replacement by —H. The aromatic sulfonic acids are hydrolyzed to hydrocarbons and sulfuric acid by heating with mineral acids.



The reaction is best carried out in sealed tubes²⁸⁶ or by superheated steam,²⁸⁷ although highly substituted aromatic sulfonic acids are hydrolyzed at 100°. The hydrolysis of sulfonic acids is chiefly of interest because of its application in the separation of hydrocarbon mixtures. A mixture of hydrocarbons or aryl halides is sulfonated and the sulfonic acids or salts isolated. Occasionally one component of the mixture is resistant to sulfonation²⁸⁸ and is separated in this way. The separation is sometimes carried out by fractional crystallization of the salts and then hydrolysis of the purified products. If one of the sulfonic acids is more readily hydrolyzed than the other,²⁸⁹ one hydrocarbon can be removed by steam distillation.

The aliphatic sulfonic acids are not hydrolyzed by acids and in this series replacement of the sulfonic group by hydrogen is not known.

Replacement by —OH. The formation of phenols by the alkaline fusion of salts of aromatic sulfonic acids was discovered²⁸⁹ simultaneously by Wurtz, Kekulé, and Dusart.



This is familiar as a commercial and laboratory²⁹⁰ method for the synthesis of phenols. It may be added that sodium hydroxide often fails as a reagent for this reaction but that then potassium hydroxide, alone or mixed with sodium hydroxide, will bring about reaction. Rearrangements often occur during fusion (e.g., both *m*- and *p*-benzenedisulfonic acids give resorcinol), and this, therefore, cannot be used to determine the orientation of substituents. Oxidation reactions²⁹¹ may cause the formation of by-products.

²⁸⁶ Limpricht, *Ber.*, **10**, 315 (1877).

²⁸⁷ Armstrong and Miller, *J. Chem. Soc.*, **45**, 148 (1884); Kelbe, *Ber.*, **19**, 92 (1886).

²⁸⁸ Cohen and Hartley, *J. Chem. Soc.*, **87**, 1362 (1904).

²⁸⁹ Wurtz, *Compt. rend.*, **64**, 749 (1867); Kekulé, *ibid.*, **64**, 752 (1867); Dusart, *ibid.*, **64**, 859 (1867).

²⁹⁰ Gattermann, *Ber.*, **24**, 2121 (1891).

²⁹¹ Liebermann, *Ann.*, **212**, 25 (1882); Meyer and Hartmann, *Ber.* **38**, 3945 (1905) Boswell and Dickson, *J. Am. Chem. Soc.*, **40**, 1786 (1918).

The aliphatic sulfonic acids are more stable than the aromatic but treatment at 350° with 4*N* alkali causes partial conversion²⁹² to alcohols.

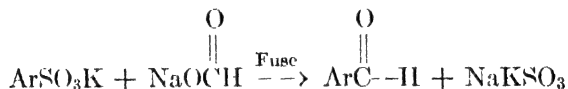
Replacement by —CN. Fusion of salts of aromatic sulfonic acids with potassium cyanide²⁹³ is a familiar method for the preparation of aryl cyanides.



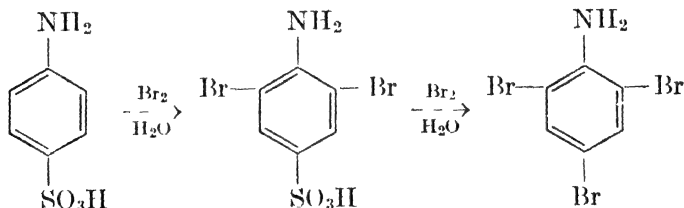
The formation of cyanohydrins from the bisulfite addition products of the aldehydes and ketones may be considered an example of an analogous reaction in the aliphatic series. The reaction does not appear to have been extensively studied with the aliphatic sulfonic acids, but α -toluenesulfonic acid²⁹⁴ gives benzyl cyanide by distillation with potassium cyanide.



Replacement by Other Groups. A number of reactions for the replacement of the sulfonic acid group have either been studied in only a few cases or are not generally applicable. Aldehydes have been obtained²⁹⁵ by fusion of sodium formate with the potassium salt of an aromatic sulfonic acid. The sodium sulfonate does not react.



Sulfanilic acid gives tribromoaniline²⁹⁶ by reaction with bromine water, but this type of replacement is limited, in the benzene series, to cases in which the sulfonic acid group is *ortho* or *para* to a phenolic or amino group.



In general, sulfonic acids derived from polycyclic aromatic hydrocarbons undergo replacement of the sulfonic acid group more readily

²⁹² Wagner and Reid, *J. Am. Chem. Soc.*, **53**, 3407 (1931).

²⁹³ Merz and Mulhäuser, *Ber.*, **3**, 710 (1870).

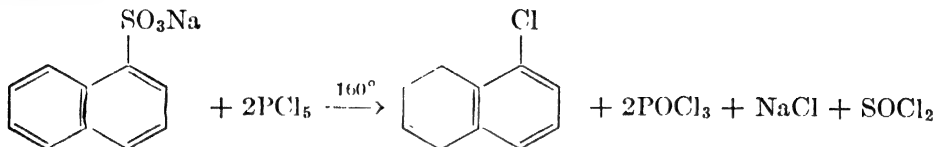
²⁹⁴ Barbaglia, *Ber.*, **5**, 270 (1872).

²⁹⁵ Meyer, *Ann.*, **156**, 273 (1870).

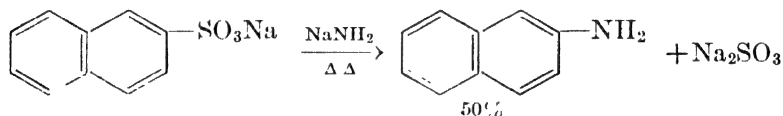
²⁹⁶ Kelbe, *Ber.*, **15**, 39 (1882); *Ber.*, **16**, 617 (1883); Kelbe *et al.*, *Ber.*, **19**, 1547 (1886); Heinichen, *Ann.*, **253**, 271 (1889); Baur, *Ber.*, **27**, 1619 (1894).

than the members of the benzene series. Some of the nitronaphthalene-sulfonic acids and anthraquinonesulfonic acids give ²⁹⁷ nitrochloronaphthalenes and chloroanthraquinones by heating with hot aqueous chlorine or with hydrochloric acid and sodium chlorate.

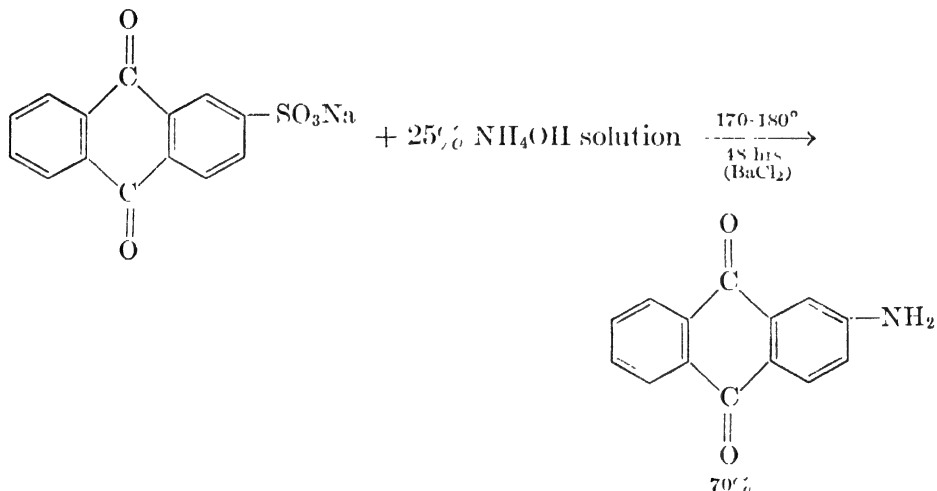
Some sulfonates undergo replacement reactions ²⁹⁸ when heated with phosphorus pentachloride.



Poor yields of aniline are obtained ²⁹⁹ by heating sodamide with sodium benzenesulfonate, but sodium β -naphthalenesulfonate and naphtholsulfonates give better results.³⁰⁰



Replacement of sulfonate groups by amino groups occurs with relative ease in the monosulfonic and disulfonic acids derived from anthraquinone.³⁰¹



²⁹⁷ Ullmann and Ochsner, *Ann.*, **381**, 2 (1911); Ger. pat. 205,913 [*Chem. Zentr.*, **I**, 702 (1909)]; Ger. pat. 228,876 [*Chem. Zentr.*, **I**, 102 (1911)]; Friedlander, Karamessinis, and Schenk, *Ber.*, **55**, 45 (1922).

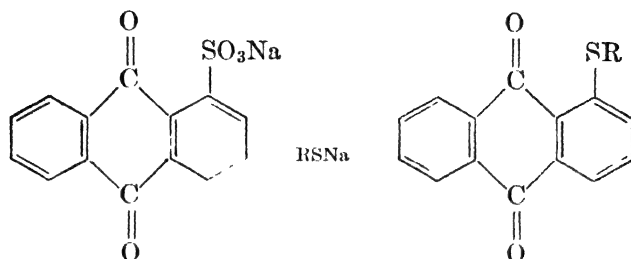
²⁹⁸ Carius, *Ann.*, **114**, 145 (1860). Under milder conditions an excellent yield of the sulfonyl chloride is obtained from sodium α -naphthalenesulfonate. See Joy and Bogert, *Ref.* 282.

²⁹⁹ Jackson and Wing, *Ber.*, **19**, 902 (1886).

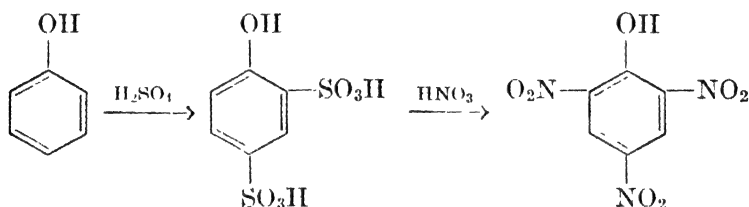
³⁰⁰ Sachs, *Ber.*, **39**, 3014 (1906).

³⁰¹ Kaufler and Imhoff, *Ber.*, **37**, 4708 (1904); Ger. pat. 256,515 [*Chem. Zentr.*, **I**, 866 (1913)]; Ger. pat. 273,810 [*Chem. Zentr.*, **I**, 1903 (1914)].

Sodium α -anthraquinonesulfonate reacts readily³⁰² with mercaptides, giving α -alkylmercaptoanthraquinones. This reaction has been applied to the preparation of solid derivatives of mercaptans.



The sulfonic acid group is often readily replaced by the nitro group; sulfonation is sometimes carried out³⁰³ before nitration because the sulfonic acids are not readily oxidized by nitric acid.



Disulfonic acids and their derivatives in which the sulfur atoms are attached to adjacent carbon atoms are cleaved by alkaline reagents³⁰⁴ similarly to ethylene disulfones (p. 883).

Reactions of Esters of Sulfonic Acids

Unless definitely stated otherwise, this discussion will deal with aliphatic esters of aromatic sulfonic acids. The aliphatic esters of aliphatic sulfonic acids have not been thoroughly investigated; their reactions appear to be sometimes similar and sometimes dissimilar to those of the alkyl esters of aromatic sulfonic acids. The reactions of the latter (ArSO_3R) lead to introduction of an alkyl group, but when aryl esters (ArSO_3Ar) react they usually³⁰⁵ form sulfinates and introduce the ArO group. In general the aryl esters are less useful in synthesis and will not be described in detail. It should perhaps be pointed out that

³⁰² Reid, Mackall, and Miller, *J. Am. Chem. Soc.*, **43**, 2104 (1921).

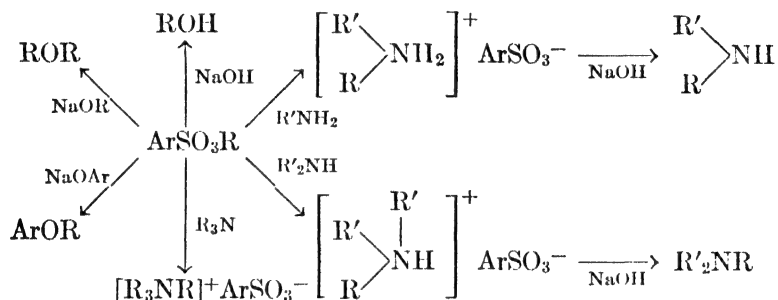
³⁰³ Merz and Zetter, *Ber.*, **12**, 2037 (1879).

³⁰⁴ Autenrieth and Rudolph, *Ber.*, **34**, 3169 (1901); Autenrieth and Koburger, *Ber.*, **36**, 3626 (1903); Kohler, *Am. Chem. J.*, **19**, 728 (1897); Clutterbuck and Cohen, *J. Chem. Soc.*, **121**, 120 (1922).

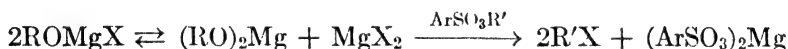
³⁰⁵ Ferns and Lapworth, *J. Chem. Soc.*, **101**, 273 (1912); Philips, *ibid.*, **123**, 44 (1923).

the sulfonic esters * contain no double bond and that this may account for the difference in their reactions and those of esters of carboxylic acids. From the same considerations outlined in the discussion of sulfones (p. 881) it would follow that reactions of carboxylic esters which occur by addition to the $>\text{C}=\text{O}$ would not occur, or would occur less readily, or by a different mechanism, with sulfonic esters.

O-, N-, S-Alkylation. Alcohols are produced by the alkaline hydrolysis of alkyl esters of sulfonic acids. In some cases³⁰⁵ hydrolysis occurs by exposure to moisture of the air. Sodium alkoxides or phenoxides give ethers.³⁰⁶ Amines^{305, 307} are alkylated by alkyl sulfonates as they are by alkyl halides.



The formation of quaternary ammonium sulfonates has been used for the identification of amines.³⁰⁸ Alkoxymagnesium halides, instead of giving ethers as do the sodium alkoxides, give alkyl halides³⁰⁹ from their reaction with alkyl esters of aromatic sulfonic acids.



The formation of sulfides (p. 854) and sulfones (p. 874) by the reactions of mercaptides and sodium sulfinates with alkyl sulfonates has already been mentioned.

* This chapter contains no separate discussion of alkyl sulfates, but their structure

$\left(\begin{array}{c} \text{O} \\ \uparrow \\ \text{ROSOR} \\ \downarrow \\ \text{O} \end{array} \right)$ is closely related to that of sulfonic esters and the reactions of the two series are

therefore comparable.

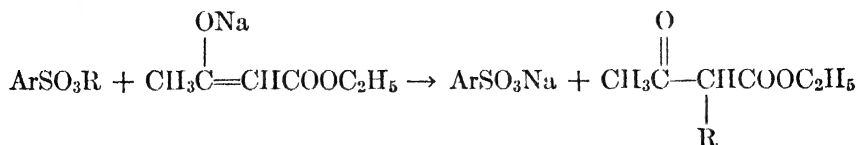
³⁰⁵ Kastle and Murrill, *Am. Chem. J.*, **17**, 290 (1895); Kastle, Murrill, and Frazer, *ibid.*, **19**, 894 (1897).

³⁰⁷ Ullmann and Wenner, *Ann.*, **327**, 120 (1903); Földi, *Ber.*, **55**, 1535 (1922).

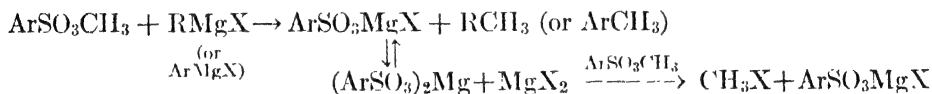
³⁰⁸ Marvel, Scott, and Amstutz, *J. Am. Chem. Soc.*, **51**, 3638 (1929).

³⁰⁹ Mine, *J. Chem. Soc. Japan*, **55**, 1168 (1934) [*C. A.*, **29**, 7940 (1935)]. Cope [*J. Am. Chem. Soc.*, **56**, 1346 (1934)] has observed a similar reaction with alkyl sulfates.

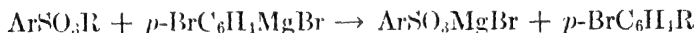
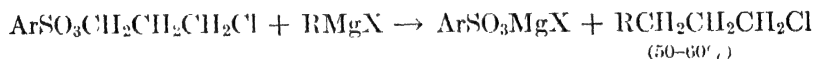
C-Alkylation. The alkyl esters of aromatic sulfonic acids appear³¹⁰ to be satisfactory reagents for the alkylation of active methylene compounds, although they have not been widely used for this purpose.



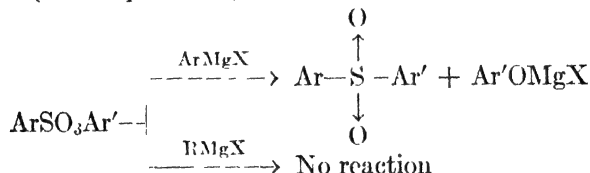
The reaction of sulfonates with Grignard reagents has been thoroughly studied.^{305, 311} Alkyl esters of aromatic sulfonic acids react with both aromatic and aliphatic Grignard reagents, giving the hydrocarbon (30-70 per cent) and halomagnesium sulfonate. The latter is responsible for the side reaction which gives alkyl halide as a by-product.



This reaction is the basis of methods for lengthening the carbon chain by three carbon atoms³¹² and for preparing *p*-alkylbromobenzenes.³¹³



Aryl esters of aromatic sulfonic acids³¹¹ do not react with alkylmagnesium halides; with arylmagnesium halides the products are diarylsulfones (40-85 per cent).



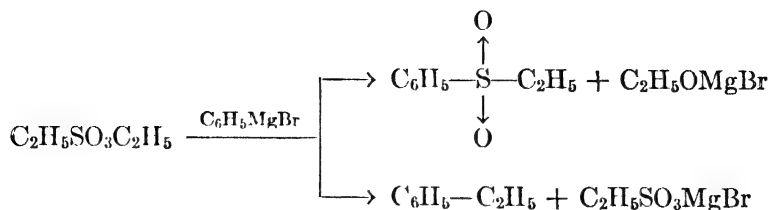
Alkyl esters of aliphatic sulfonic acids³⁰⁵ give both types of the reactions described above. Ethyl ethanesulfonate reacts with phenylmagnesium bromide to give a sulfone as the major product, although some ethylbenzene is formed.

³¹⁰ Nair and Peacock, *J. Indian Chem. Soc.*, **12**, 318 (1935) [*C. A.*, **29**, 6881 (1935)].

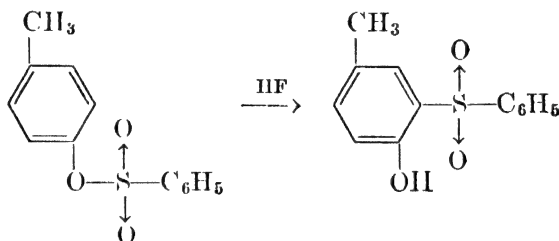
³¹¹ Gilman and Beaber, *J. Am. Chem. Soc.*, **47**, 520 (1925); Gilman, Beaber, and Myers, *ibid.*, **47**, 2047 (1925); Gilman and Heck, *ibid.*, **50**, 2223 (1928); Mine, *J. Chem. Soc. Japan* **55**, 1087 (1934) [*C. A.*, **29**, 5427 (1935)].

³¹² Rossander and Marvel, *J. Am. Chem. Soc.*, **50**, 1491 (1928).

³¹³ Copenhaver, Roy, and Marvel, *ibid.*, **57**, 1311 (1935).

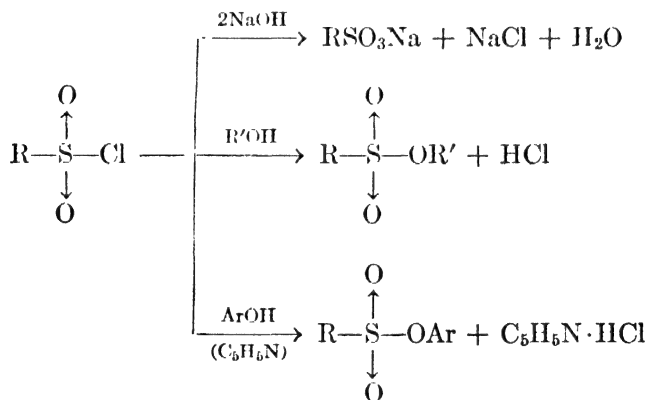


Fries Rearrangement. The formation ³¹⁴ of a sulfone from the treatment of *p*-tolyl benzenesulfonate with anhydrous hydrogen fluoride is analogous to the well-known Fries rearrangement of aryl esters of carboxylic acids.



Reactions of Sulfonyl Halides

With —OH Compounds. Sulfonyl halides are hydrolyzed slowly by water, rapidly by alkali. They react readily with alcohols ³¹⁵ to give esters. Aryl esters are prepared by using a salt of the phenol or, better, by the use of pyridine ³¹⁶ as a solvent.



With Amines. The most common use of the reaction of amines with sulfonyl halides is in the familiar Hinsberg test ³¹⁷ for distinguishing

³¹⁴ Simons, Archer, and Randall, *ibid.*, **62**, 485 (1940).

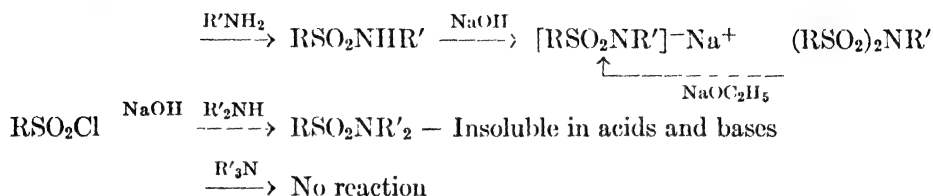
³¹⁵ Krafft and Roos, *Ber.*, **25**, 2255 (1892); **26**, 2823 (1893); Krafft, *Ber.*, **26**, 2829 (1893)

³¹⁶ Sekera and Marvel, *J. Am. Chem. Soc.*, **55**, 345 (1933); Sekera, *ibid.*, **55**, 421 (1933)

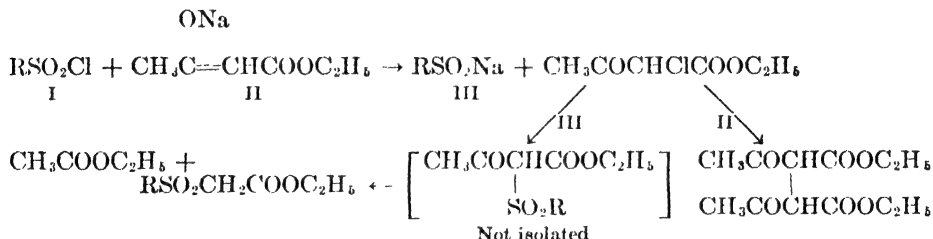
Hazlet, *ibid.*, **59**, 287 (1937).

³¹⁷ Hinsberg, *Ber.*, **23**, 2963 (1890); Hinsberg and Kessler, *Ber.*, **38**, 906 (1905).

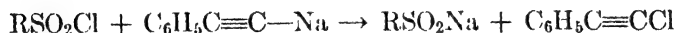
primary, secondary, and tertiary amines. The reaction may also be applied to the separation of amine mixtures and to characterization of amines or sulfonyl chlorides. In the case of primary amines, disulfonyl derivatives are sometimes important by-products, but these may be converted to simple sulfonamides by alcoholysis in the presence of sodium ethoxide.



With Enolates of Active Methylene Compounds. When *p*-toluenesulfonyl chloride is allowed to react with the sodium derivative of ethyl acetoacetate,³¹⁸ it appears that the first step is reduction of the chloride to the sulfinate; subsequent reactions lead to the formation of tolylsulfonylacetate ester and diacetylsuccinic ester. Similar results are reported with malonic ester.



With Organometallic Compounds. The activity of sulfonyl halides as halogenating agents, shown above, is also observed in their reactions with zinc alkyls³¹⁹ and sodium acetylides,³²⁰ which produce replacement of metal by halogen.



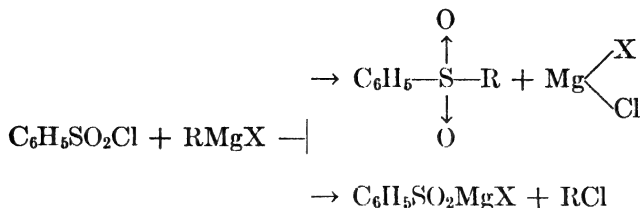
The reaction of sulfonyl chlorides with an equivalent amount of the Grignard reagent³²¹ at low temperatures gives sulfones (up to 35 per cent) as well as products analogous to those from other organometallic compounds.

³¹⁸ Kohler and MacDonald, *Am. Chem. J.*, **22**, 219, 225 (1899).

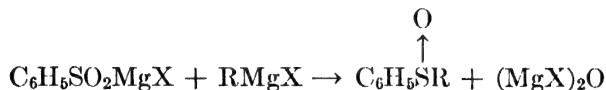
³¹⁹ Otto and Troger, *Ber.*, **24**, 488 (1891).

³²⁰ Truchet, *Ann. chim.*, **16**, 390 (1931); Murray, *J. Am. Chem. Soc.*, **60**, 2662 (1938).

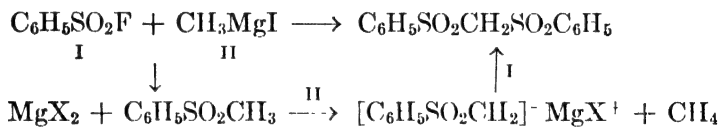
³²¹ Gilman and Fothergill, *J. Am. Chem. Soc.*, **51**, 3501 (1929).



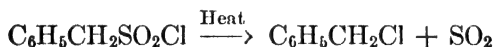
When the sulfonyl chlorides are treated with an excess of the Grignard reagent, then gently heated, the sulfinate is converted to sulfoxide and other products.^{321, 322}



The reaction of sulfonyl fluorides with the Grignard reagent has been the subject of a controversy.³²³ The formation of sulfones and disulfones has been reported.



Other Reactions. The reaction of sulfonyl halides with mercaptans and thiophenols is not analogous to the reaction with alcohols and phenols and will be considered in the section on thiolsulfonic esters. The preparation of thiophenols (p. 844) and sulfinic acids (p. 914) by the reduction of sulfonyl halides is described elsewhere. Aliphatic sulfonyl chlorides form α -halo derivatives³²⁴ by a reaction analogous to the Hell-Volhard-Zelinsky synthesis. Some sulfonyl halides decompose upon standing or under the influence of heat; α -toluenesulfonyl chloride,³²⁵ for example, gives benzyl chloride and sulfur dioxide.



Reactions of Sulfonamides

Hydrolysis. In discussing the Hinsberg reaction (p. 899) it was mentioned that an important application was the separation of amines. The amines may usually be recovered from their sulfonamides in good

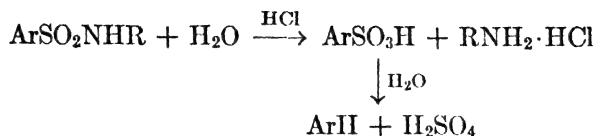
³²² Hepworth and Clapham, *J. Chem. Soc.*, **119**, 1188 (1921); Wedekind and Schenk, *Ber.*, **54**, 1604 (1921).

³²³ Steinkopf and Jaeger, *J. prakt. Chem.*, **128**, 63 (1930); Gibson, *ibid.*, **142**, 218 (1935)

³²⁴ Latimer and Bost, *J. Org. Chem.*, **5**, 24 (1940).

³²⁵ Limpricht, *Ber.*, **6**, 534 (1873); Mohr, *Ann.*, **221**, 215 (1883).

yields (90–95 per cent) by refluxing (ten to thirty-six hours) with 25 per cent hydrochloric acid.³²⁶



α -Toluenesulfonamides are very readily hydrolyzed and are therefore useful in synthesis.³²⁷



Sulfonamides obtained from secondary amines undergo this reaction more readily than those from primary amines. Acid hydrolysis of nitrobenzenesulfonamides is extremely difficult.

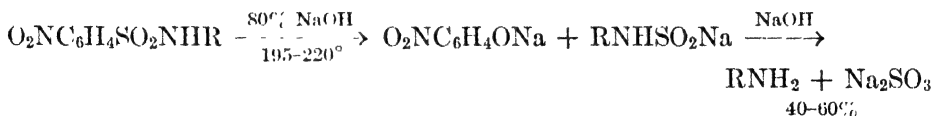
The reaction of sulfonamides with cold aqueous alkali to form salts is a familiar one (see p. 899). The acidity of sulfonamides may be at-

tributed to the electron-attracting properties of the $\text{R}-\text{S}-\text{O}$ group, and

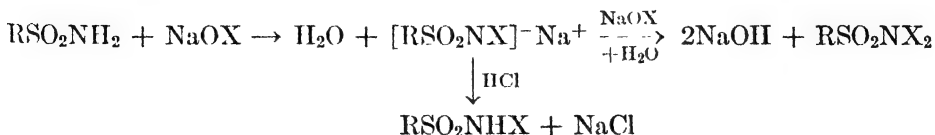
$$\begin{array}{c} \text{O} \\ \uparrow \\ \text{R}-\text{S}-\text{O} \\ \downarrow \\ \text{O} \end{array}$$

the structure of the anion is subject to the same considerations advanced in the discussion of sulfones (p. 880) except that N replaces C.

Most sulfonamides are not changed by drastic treatment with alkali (e.g., benzenesulfonanilide is unaffected by fusion with 80 per cent sodium hydroxide at 250°), but the presence of a nitro group in the *ortho* or *para* position causes them to undergo alkaline hydrolysis.^{271, 328} Cleavage occurs between sulfur and carbon, rather than between sulfur and nitrogen as is the case in acid hydrolysis.



Halogenation. Sulfonamides react readily³²⁹ with halogen in alkaline solution to give N-halo and N,N-dihalo derivatives.



³²⁶ Schreiber and Shriner, *J. Am. Chem. Soc.*, **56**, 1618 (1934).

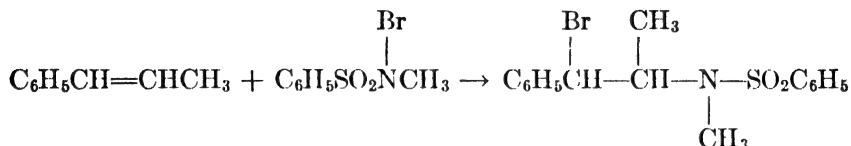
³²⁷ Johnson and Ambler, *J. Am. Chem. Soc.*, **36**, 372 (1914); Johnson and Bailey, *J. Am. Chem. Soc.*, **38**, 2135 (1916).

³²⁸ Pezold, Schreiber, and Shriner, *J. Am. Chem. Soc.*, **56**, 696 (1934).

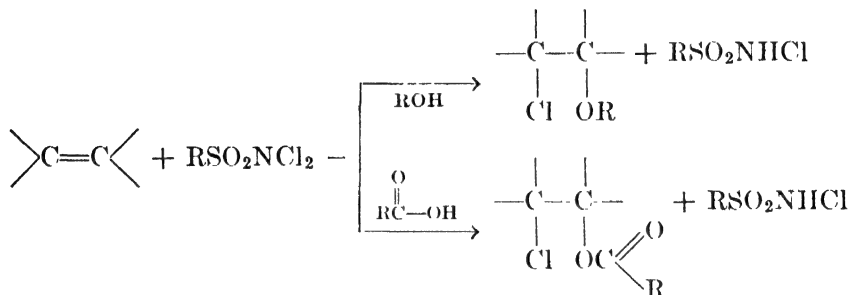
³²⁹ Chattaway, *J. Chem. Soc.*, **87**, 148 (1905).

"Chloramine-T" (sodium N-chloro-*p*-toluenesulfonamide), "Dichloramine-T" (N,N-dichloro-*p*-toluenesulfonamide), and "Halozone" (*p*-HOOC₆H₄SO₂NCl₂) are useful antiseptics. The halogen of N-halosulfonamides is "positive" in character; it is therefore remarkable that a salt such as Chloramine-T ($[\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{NCl}]^-\text{Na}^+$) should be stable.

The N-halosulfonamides add to olefins,³³⁰ forming β -halosulfonamides.

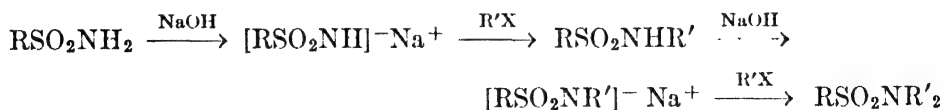


By carrying out the reaction in the presence of alcohols or acids the main products are β -halogen ethers (80-95 per cent) or esters.



Dihalides and β -chlorosulfonamides are by-products of these reactions. In the reaction of unsymmetrical olefins with N-bromo-N-alkylsulfonamides the bromine atom takes the same position as in the "normal" addition (Markownikoff's rule) of hydrogen bromide, but with N,N-dibromoamides "abnormal" addition occurs.³³¹

Alkylation. The salts of sulfonamides or N-alkylsulfonamides are alkylated by alkyl halides³³² or alkyl sulfates.³³³



This reaction is useful in the synthesis of amines.³³⁴

³³⁰ Földi, *Ber.*, **63**, 2257 (1930); Likhoshesterov *et al.*, *J. Gen. Chem. (U.S.S.R.)*, **8**, 370 (1938); *ibid.*, **9**, 2000, 2012, 2085 (1939); *Acta Univ. Voronegiensis*, **9**, No. 3 (1937) [*C. A.*, **32**, 5369 (1938); **34**, 4380, 4381, 3673 (1940); **32**, 7018 (1938)].

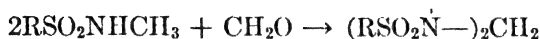
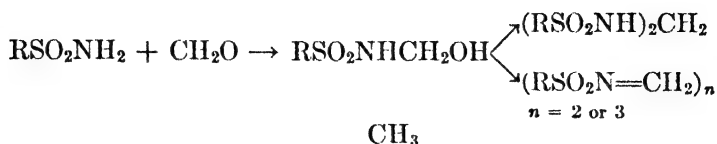
³³¹ Kharasch and Priestley, *J. Am. Chem. Soc.*, **61**, 3425 (1939).

³³² Hinsberg and Strupler, *Ann.*, **287**, 222 (1895).

³³³ Pschorr and Karo, *Ber.*, **39**, 3140 (1906).

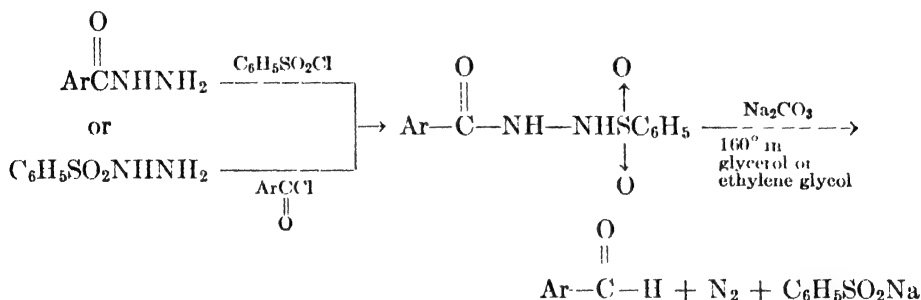
³³⁴ Carothers, Bickford, and Hurwitz, *J. Am. Chem. Soc.*, **49**, 2908 (1927).

Reaction with Aldehydes. Either acids³³⁵ or bases³³⁶ catalyze the reaction of sulfonamides and N-alkylsulfonamides with aldehydes. The types of products formed may be illustrated with formaldehyde.

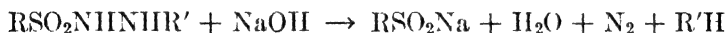


A variety of aldehydes have been used in this reaction.³³⁷ Synthetic resins may be so obtained.³³⁶

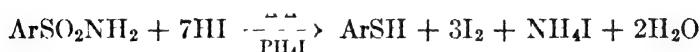
Sulfonhydrazides. Alkaline hydrolysis of N-acyl sulfonhydrazides has been applied³³⁷ to the synthesis of aromatic aldehydes; aliphatic aldehydes cannot be prepared by this method.



N-Alkylsulfonhydrazides give hydrocarbons upon hydrolysis.³³⁸



Other Reactions. The sulfonamides, sulfonyl chlorides, and thiol-sulfonic esters are the only sulfonic acid derivatives which can be reduced. The reduction³³⁹ of sulfonamides requires hydriodic acid in a sealed tube with phosphonium iodide as a catalyst.



³³⁵ McMaster, *ibid.*, **56**, 204 (1934).

³³⁶ Can. pat. 303,697 [*C. A.*, **24**, 5518 (1930)].

³³⁷ Walter *et al.*, *Kolloid Beihefte*, **40**, 1, 29, 45 (1934) [*C. A.*, **28**, 7560 (1934)]; Hug, *Bull. soc. chim.*, [5] **1**, 990 (1934), MacFayden and Stevens, *J. Chem. Soc.*, 584 (1936); Buchman and Richardson, *J. Am. Chem. Soc.*, **61**, 891 (1939); Natelson and Gottfried, *ibid.*, **63**, 487 (1941).

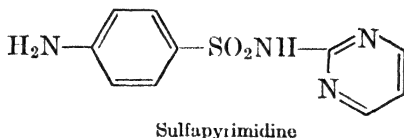
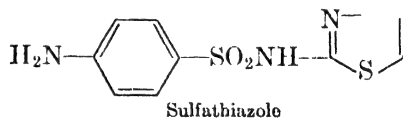
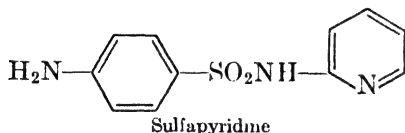
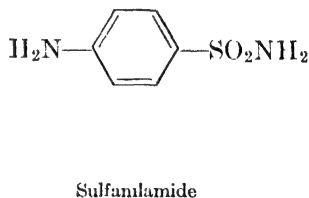
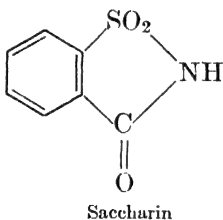
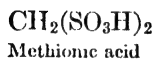
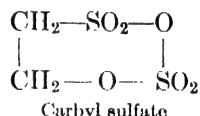
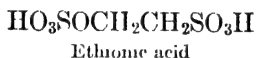
³³⁸ Arndt and Scholz, *Ann.*, **510**, 62 (1934); Coffey, *J. Chem. Soc.*, 637 (1926).

³³⁹ Fischer, *Ber.*, **48**, 93 (1915).

Sulfonamides react with nitrous acid³⁴⁰ and diazonium salts.^{340, 341} Sulfonazides are mentioned elsewhere (p. 929).

Specific Sulfonic Acid Derivatives of Importance

The formation of isethionic acid, ethionic acid, and carbyl sulfate has been discussed in Chapter 3. Methionic acid behaves as an active methylene compound.³⁴² Taurine occurs in combination as taurocholic acid in the bile. Sodium iodomethanesulfonate (Abrodil) is opaque to x-rays and is therefore useful in x-ray therapy. Saccharin is a sulfonimide. Compounds of great medicinal importance are sulfanilamide, sulfapyridine, sulfathiazole, and sulfapyrimidine (sulfadiazine), which are useful as specifics for streptococic, pneumococic, and other infections.³⁴³



³⁴⁰ Hinsberg, *Ber.*, **27**, 598 (1894).

³⁴¹ Key and Dutt, *J. Chem. Soc.*, 2035 (1928).

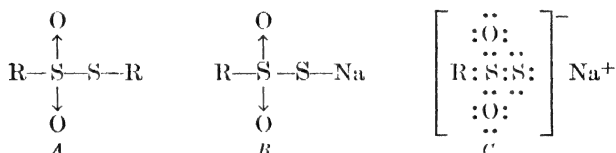
³⁴² Schroter and Herzberg, *Ber.*, **38**, 3393 (1905); Franchimont and Klobbie, *Rec. trav. chim.*, **9**, 233 (1890).

³⁴³ Northey, *Chem. Rev.*, **27**, 85 (1940). This contains a comprehensive survey of about 200 references to compounds of the sulfanilamide type which are of chemotherapeutic interest.

X. THIOLSULFONATES *

General Characteristics

Thiosulfonic acids are unknown but their salts and alkyl derivatives, considered here as esters, may be prepared. The structure of the esters, which are also called disulfoxides, will be considered after their chemistry has been discussed, but in the meantime they will be assumed to have the structure *A*. The structure of the salts will be written as in *B*. This is an arrangement of convenience and is adopted because the divalent sulfur is involved in most of the reactions of the salts. The convention should not be regarded as having any more specific meaning, since in the thiosulfonate anion (*C*) the electronic configurations of the divalent sulfur and of oxygen are similar.



The salts are crystalline, water-soluble solids. The lower-molecular-weight alkyl esters of alkanethiosulfonic acids³⁴⁴ are liquids heavier than water, with a very unpleasant odor. They cannot be distilled without decomposition but may be steam-distilled. Those of high molecular weight are odorless solids.³⁴⁵ The aryl esters of aromatic thiosulfonic acids^{344, 346} are usually crystalline solids. Some of these compounds³⁴⁷ become colored upon exposure to light but become colorless again upon standing in the dark (phototropy). This phenomenon is attributed³⁴⁷ to the presence of small amounts of disulfides as impurities.

* The name "thiosulfonate" is used here in the nomenclature of the esters because of the analogy with thiol esters of carboxylic acids (p. 930). Theoretically, other thio (but

not thiol) sulfonic esters are possible $\left(\begin{array}{c} \text{O} \\ \uparrow \\ \text{R}-\text{S}-\text{OR} \\ \downarrow \\ \text{S} \end{array} \right)$. The structure of the salts (formula *C*

above) is such that their designation as thiol or thion derivatives would be meaningless, and the salts are therefore named as thiosulfonates.

³⁴⁴ Otto, *Ber.*, **15**, 121 (1882).

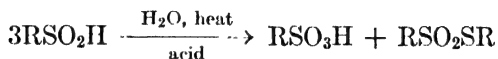
³⁴⁵ Otto, *Ann.*, **145**, 13, 317 (1868); Fromm and Palma, *Ber.*, **39**, 3308 (1906); Hilditch, *J. Chem. Soc.*, **97**, 1091 (1910).

³⁴⁶ Bere and Smiles, *J. Chem. Soc.*, **125**, 2359 (1924); Gauntlett and Smiles, *ibid.* **127**, 2746 (1925).

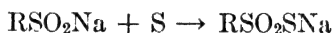
³⁴⁷ Child and Smiles, *ibid.*, 2696 (1926).

Methods of Preparation

From Sulfinic Acids. Free sulfinic acids decompose * slowly, giving sulfonic acids and thiosulfonic esters. The decomposition may be hastened³⁴⁴ by heat and aqueous acid and the reaction is used for the preparation^{345, 348} of thiosulfonic esters.



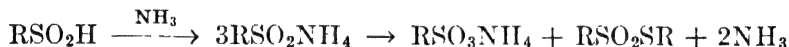
The sodium salts of thiosulfonic acids may be obtained³⁴⁹ from the reaction of solutions of the sodium salts of sulfinic acids with sulfur.



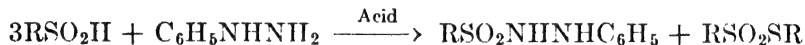
The sodium or potassium thiosulfonates give the corresponding esters when treated^{344, 350} with reactive alkyl halides or alkyl sulfates.



The ammonium salts of sulfinic acids decompose,³⁵¹ giving products similar to those obtained from the free acids.



This is also similar to the reaction³⁵² of phenylhydrazine with sulfinic acids.



The silver salts of sulfinic acids, prepared from the reaction of the sodium salts with silver nitrate, react^{347, 353} with sulfenyl halides to give thiosulfonic esters.



The silver sulfinates are generally not stable in air for long periods of time and should be prepared immediately before use. This method appears well suited for the synthesis of unsymmetrical thiol esters, including aryl derivatives which cannot be obtained from the sodium thiosulfonates by the other methods described above.

* It is reported, however, that pure sulfinic acids may be stored in a desiccator without decomposition. [Autenrieth, *Ann.*, **259**, 362 (1890).]

³⁴⁸ Smiles and Gibson, *ibid.*, **125**, 180 (1924); v. Braun and Weissbach, *Ber.* **63**, 2836 (1930).

³⁴⁹ Troeger and Grothe, *J. prakt. Chem.*, [2] **56**, 473 (1897).

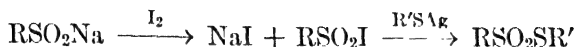
³⁵⁰ Gibson, *J. Chem. Soc.*, 2637 (1931).

³⁵¹ Hälssig, *J. prakt. Chem.*, [2] **56**, 213 (1894).

³⁵² Escalas, *Ber.*, **18**, 893 (1885).

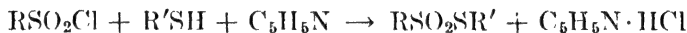
³⁵³ Gibson, Miller, and Smiles, *J. Chem. Soc.*, **127**, 1821 (1925).

From Sulfonyl Halides. Unsymmetrical thiolsulfonic esters may also be prepared satisfactorily (80–90 per cent) by the reaction of sulfonyl iodides with silver mercaptides.^{347, 353}



In the more reactive sulfonyl iodides, decomposition may liberate free iodine which oxidizes the mercaptide to the disulfide. The method therefore gives the best results when stable sulfonyl iodides are used and when the corresponding disulfide is soluble in water and therefore readily removed.

It should perhaps be mentioned at this point that the reaction of sulfonyl chlorides with sulfhydryl compounds is not generally³⁵⁴ a satisfactory method for the preparation of thiolsulfonic esters, although small yields (up to 25 per cent) may be obtained in the presence of pyridine.³⁵³

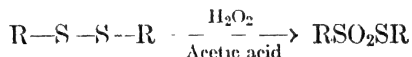


The chief products of the reaction are usually sulfinic acid (RSO_2H) and disulfide (R'SSR'). It is likely that the ester is the precursor of these but that it reacts with the mercaptan (p. 908) to give the chief products.

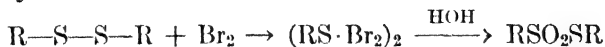
Salts of thiosulfonic acids are obtained^{349, 350, 355} from the reaction of sulfonyl chlorides with sodium sulfide. The reaction occurs in two stages. The first is the reduction of the sulfonyl chloride to sulfinic acid with precipitation of finely divided sulfur. Upon heating the solution the sulfur slowly dissolves with the formation of a thiosulfonate.



From Disulfides. Cautious oxidation of disulfides with hydrogen peroxide at room temperature produces thiolsulfonic esters.³⁵⁶



Tetrahalides of some disulfides may be obtained by the reaction of the disulfides with bromine or iodine. These are hydrolyzed³⁵⁷ to thiolsulfonic esters by water or silver nitrate.



³⁵⁴ However, see Kohlhusé, *J. Am. Chem. Soc.*, **54**, 2441 (1932).

³⁵⁵ Spring, *Ber.*, **7**, 1157 (1874); Otto, *Ber.*, **13**, 1282 (1880); Fromm and Erfurt, *Ber.*, **42**, 3816 (1909).

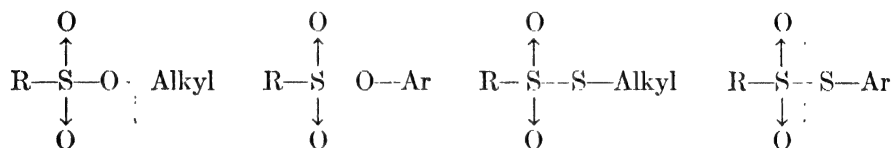
³⁵⁶ Hinsberg, *Ber.*, **41**, 2836 (1908); *Ber.*, **42**, 1278 (1909); Kolhatkar and Bokil, *J. Indian Chem. Soc.*, **7**, 843 (1930) [*C. A.*, **25**, 2126 (1931)].

³⁵⁷ Fromm, *Z. angew. Chem.*, **24**, 1125 (1911).

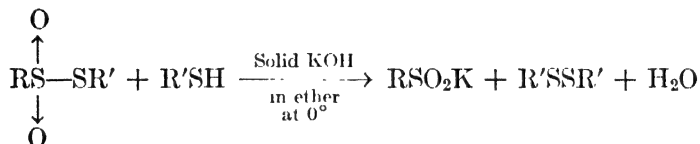
* **Other Methods.** The hydrolysis of sulfenyl chlorides or sulfenic esters (p. 921) gives thiolsulfonic esters, but the reaction is not suited for preparative work because half of the product is a disulfide, which is difficult to separate from the thiolsulfonic ester. Oxidation of mercaptans by nitric acid was the earliest method³⁵⁸ for the preparation of these compounds. Thiolsulfonic esters are among the products of electrolytic oxidation³⁵⁹ of sulfides, disulfides, and sulfoxides. Retene-sulfonyl chloride gives the thiol ester³⁶⁰ by treatment with zinc dust in benzene. Thiolsulfonic esters are among the products obtained by (1) the reaction of the salt of a thiolsulfonic acid with ethyl chlorocarbonate,³⁶¹ (2) hydrolysis of sulfonyl iodides,³⁶² and (3) treatment of *m*-nitrobenzenesulfonyl chloride with aluminum chloride in carbon disulfide.³⁶³

Reactions

In most of their reactions, thiolsulfonic esters are thioalkylating agents. The cleavage of both alkyl thiolsulfonates and aryl thiolsulfonates, therefore, is comparable to that of aryl esters of sulfonic acids.



With Sulfhydryl Compounds. Sulfhydryl compounds,³⁶⁴ sodium or potassium mercaptides,³⁶⁵ or zinc mercaptides³⁶⁴ react with thiolsulfonic esters to give disulfides.



This reaction is probably responsible for the difficulties already noted in the preparation of thiolsulfonic esters from reactions using mercaptans or mercaptides.

³⁵⁸ Märcker, *Ann.*, **136**, 83 (1865).

³⁵⁹ Fichter and Sjöstedt, *Ber.*, **43**, 3422 (1910); Fichter and Wenk, *Ber.*, **45**, 1373 (1912).

³⁶⁰ Hasselstrom and Bogert, *J. Am. Chem. Soc.*, **57**, 1579 (1935).

³⁶¹ Otto and Rössing, *Ber.*, **24**, 1147 (1891).

³⁶² Otto and Tröger, *Ber.*, **24**, 478 (1891).

³⁶³ Limpricht, *Ann.*, **278**, 239 (1895).

³⁶⁴ Pauly and Otto, *Ber.*, **10**, 2181 (1877).

³⁶⁵ Gilman, Smith, and Parker, *J. Am. Chem. Soc.*, **47**, 851 (1925).

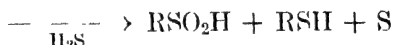
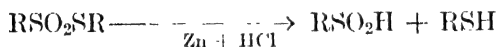
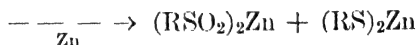
Hydrolysis. Treatment of thiolsulfonic esters with dilute aqueous alkali³⁶⁶ gives sulfinates and disulfides. Sulfenic acids may be intermediate products (*cf.* p. 921).



With Grignard Reagents. Under mild conditions (so that the initial cleavage products are not further attacked) both aliphatic and aromatic Grignard reagents give sulfinates and sulfides when they are allowed to react with thiolsulfonic esters.^{366, 367}



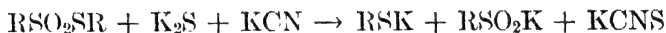
Reduction. The common occurrence of sulfinic acids among the cleavage products of the reactions already discussed is indicative of the ease of reduction of thiolsulfonic esters. Metallic zinc,^{344, 368} zinc in the presence of acid,^{344, 345, 368} and hydrogen sulfide³⁶⁹ also cause reduction.



The formation of the salt of a thiosulfonic acid from the reaction of the ester with potassium sulfide³⁷⁰ need not be considered a type of reaction different from the others but may be due to the reaction of the salt of the sulfinic acid with sulfur.



In the presence of potassium cyanide,³⁷¹ the thiosulfonate is not formed.



Other reagents which have been reported to reduce thiolsulfonic esters are hydrobromic and hydriodic acids³⁷² and sodium arsenite.³⁷¹

³⁶⁶ Pauly and Otto, *Ber.*, **11**, 2073 (1878); Otto and Rössing, *Ber.*, **19**, 1235 (1886); Zincke, *Ann.*, **391**, 55 (1912); *Ann.*, **400**, 1 (1913); *Ann.*, **406**, 103 (1914). See also Fromm and Erfurt, *Ref.* 355.

³⁶⁷ Miller and Smiles, *J. Chem. Soc.*, **127**, 224 (1925).

³⁶⁸ Otto, *Ber.*, **13**, 1282 (1880); Pauly and Otto, *Ber.*, **10**, 2181 (1877); Otto and Rössing, *Ber.*, **20**, 2079 (1887).

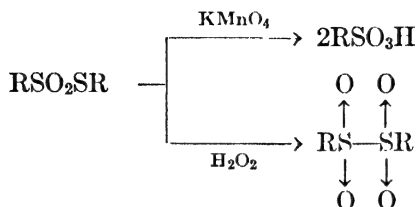
³⁶⁹ Otto and Rössing, *Ber.*, **20**, 2090 (1887); Smythe and Forster, *J. Chem. Soc.*, **97**, 1199 (1910).

³⁷⁰ Otto and Rössing, *Ber.*, **19**, 3129 (1886).

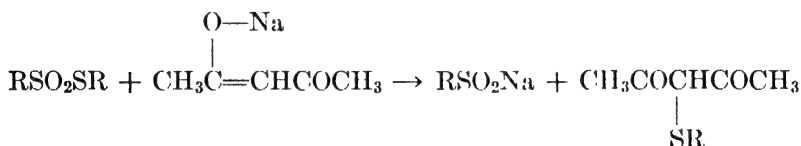
³⁷¹ Gutmann, *Ber.*, **47**, 635 (1914).

³⁷² Fries and Schürmann, *Ber.*, **47**, 1195 (1914). See also Fromm, *Ref.* 357.

Oxidation. Oxidation of thiolsulfonic esters by permanganate in glacial acetic acid ³⁴⁴ gives sulfonic acids. α -Disulfones ³⁶⁵ are formed when hydrogen peroxide in acetic anhydride is used as an oxidizing agent.

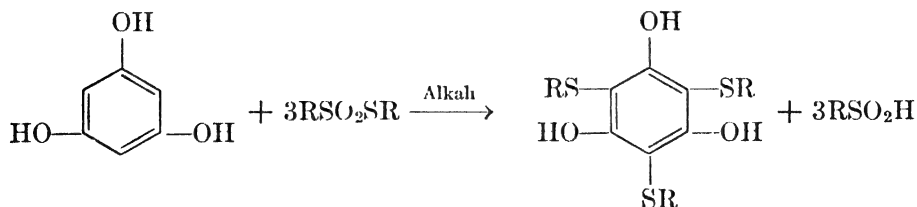


With Active Methylene Compounds. The sodium derivatives of some enols undergo thioalkylation ^{373, 374} by the action of thiolsulfonic esters. The reaction may be illustrated with acetylacetone.



A second thioalkyl group may be introduced. A variety of active methylene compounds, including disulfonylmethanes, have been subjected to this reaction. In some cases the reaction gives disulfides,³¹⁸ as would be expected from the action of alkaline reagents upon thiolsulfonic esters. In these cases sodium carbonate or sodium acetate may be active enough to bring about reaction between the active methylene compound and the thiol esters. This reaction has been useful for the synthesis of many compounds ³⁷⁴ which cannot be obtained by other methods.

With Phenols. The salts of simple phenols cause formation of disulfides from thiolsulfonic esters, in accord with the usual behavior of alkaline reagents. However, the dihydroxy and trihydroxybenzenes, naphthols, and hydroxyquinolines undergo thioalkylation, giving sulfides.^{373, 375}

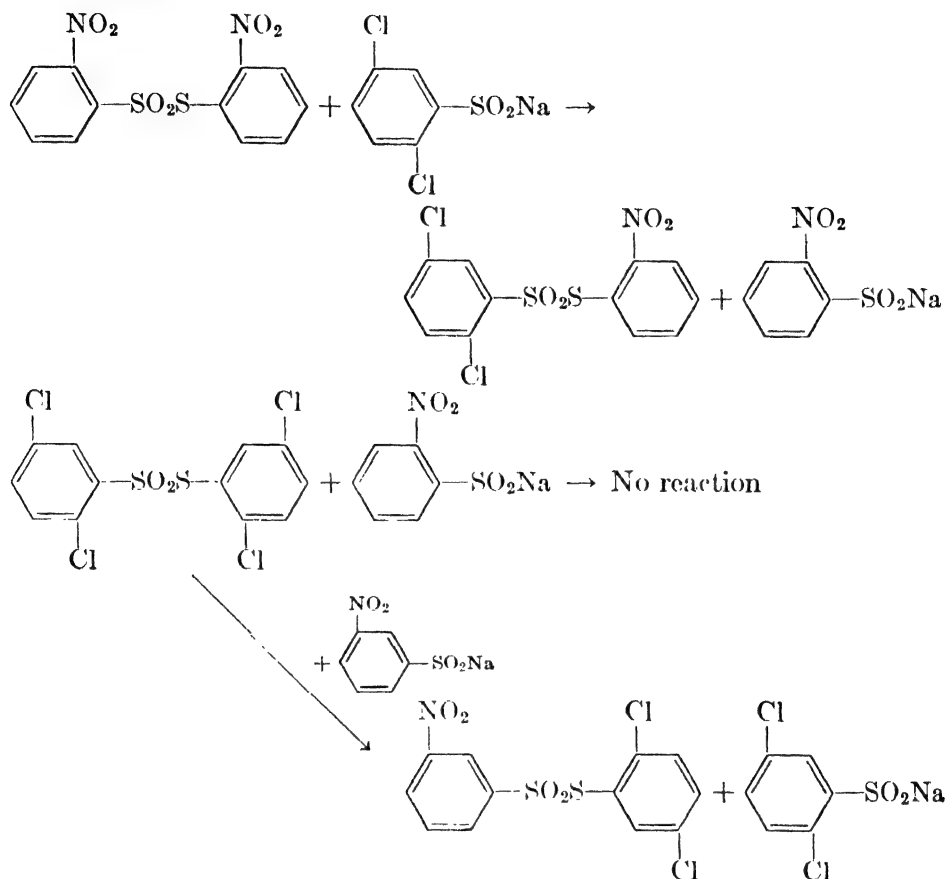


³⁷³ Brooker and Smiles, *J. Chem. Soc.*, 1723 (1926).

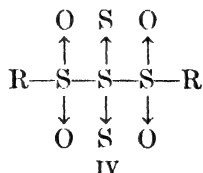
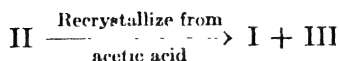
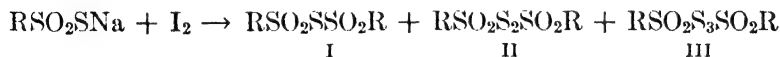
³⁷⁴ Chivers and Smiles, *ibid.*, 697 (1928); Gibson, *ibid.*, 2637 (1931); *ibid.*, 1819 (1932); Cowie and Gibson, *ibid.*, 306 (1933); 46 (1934); Gibson and Loudon, *ibid.*, 487 (1937); Gibson, *J. Am. Chem. Soc.*, **55**, 2611 (1933); Gibson, *J. Chem. Soc.*, 983 (1938).

³⁷⁵ Stevenson and Smiles, *J. Chem. Soc.*, 718 (1931).

Sulfonyl Interchange. Thiosulfonates react with salts of sulfinic acids with an interchange of sulfonyl groups.³⁷⁶ As shown below, the reaction does not always occur but depends upon the relative reactivities of the compounds involved.



Other Reactions. The salts of thiosulfonic acids are converted to thioanhydrides of sulfonic acids by the action of iodine.³⁷⁷ These may also be regarded as oxidation products of polysulfides, which they resemble in their ease of interconversion.



³⁷⁶ Loudon and Livingston, *ibid.*, 896 (1935).

³⁷⁷ Otto and Tröger, *Ber.*, **24**, 1125 (1891).

Although recent work is lacking on the structure of these products, comparison with the polysulfides (p. 864) suggests a linear arrangement in III of three sulfur atoms with all three completely coordinated (IV).

The nature of the action of phosphorus trichloride ³⁴⁵ with thiolsulfonic esters has not been completely established. The condensations brought about by treatment with concentrated sulfuric acid ³⁷⁸ and the products obtained by thermal decomposition, ³⁷⁹ with and without acetic anhydride, have been investigated in detail.

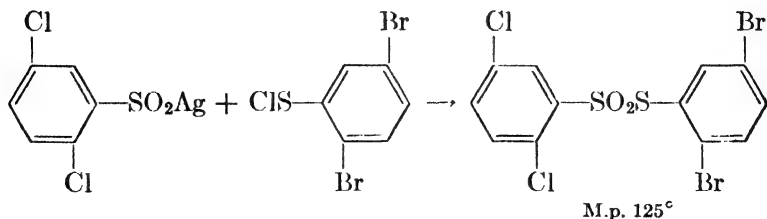
Structure of Thiolsulfonic Esters

The foregoing discussion assumed the structure of the members of this series to be that of thiolsulfonic esters. They have also been regarded as mixed anhydrides (I) ³⁷⁵ and as symmetrical disulfoxides (II).



Measurements of the optical rotatory power of unsymmetrical disulfoxides ³⁴⁵ derived from camphor ($\text{Cam}-\text{S}_2\text{O}_2-\text{R}$) are interpreted as showing that when the two groups are different the thiolsulfonate structure is correct ($\text{Cam}-\text{SO}_2\text{SCH}_3$) but that when they are similar the disulfoxide structure is correct ($\text{Cam}-\text{SO}-\text{SO}-\text{Cam}$). Results with the derivative from cystine ³⁸⁰ (p. 1132) are also interpreted on the basis of the disulfoxide structure.

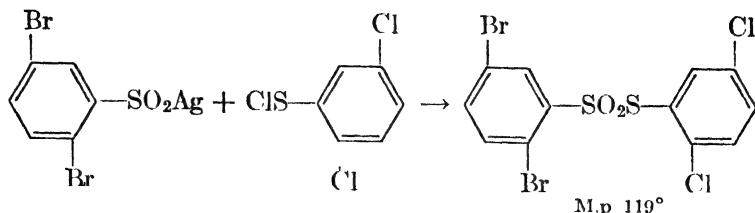
The usual reactions of this series can best be explained on the basis of the thiolsulfonic ester structure. Space does not permit a detailed discussion of the pertinent data, but a few points are worthy of mention. Isomeric products may be obtained ³⁶⁷ by the reaction of the appropriate sulphenyl chlorides with silver sulfates.



³⁷⁸ Hilditch, *J. Chem. Soc.*, **99**, 1091 (1911).

³⁷⁹ Smythe, *ibid.*, **121**, 1400 (1922).

³⁸⁰ Toennies and Lavine, *J. Biol. Chem.*, **113**, 571, 583 (1936).



These isomers have different chemical and physical properties. In reactions involving thioalkylation (e.g., of active methylene compounds) the RS— group introduced is that originally present in the sulfonyl chloride. No evidence of the introduction of different groups (from RSOSOR') is noted. These indications of an unsymmetrical structure * are also borne out ³⁶⁵ by the reaction with Grignard reagents. The anhydride structure seems unlikely in view of the formation of thiolsulfonic esters from sul-

fonyl chlorides and iodides, in which the structure $\text{R}-\text{S}-\text{X}$ is unquestioned.

XI. SULFINIC ACIDS AND THEIR DERIVATIVES

General Characteristics

There are relatively few references to aliphatic sulfinic acids,[†] and some of the fairly simple members of the series are unknown. The aliphatic sulfinic acids are thick oils which decompose rapidly and are generally isolated as zinc, barium, or other salts. The aromatic sulfinic acids, though apparently more stable than the aliphatic, decompose upon long standing (p. 906) and are slowly oxidized to sulfonic acids when exposed to air. They are weaker acids than the corresponding sulfonic acids and are less soluble in water. The free aromatic sulfinic acids may usually be obtained by acidifying aqueous solutions of their salts. The

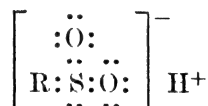
* The only other explanations would be (1) that the two products are diastereoisomers resulting from two asymmetric S atoms (p. 122), one isomer being formed preferentially by each method of synthesis, and (2) that they also react differently. While these conditions might be true in isolated cases, it seems unlikely that they could be true quantitatively in the large numbers of representatives of the series known. The behavior of the Grignard reagent (see Ref. 365) is additional evidence against these assumptions.

† The sulfinic acids and the radicals derived from them are named analogously to the sulfonic acids (see footnote on p. 886). Thus: $\text{C}_2\text{H}_5\text{SO}_2\text{H}$, ethanesulfinic acid;

$\text{C}_2\text{H}_5-\overset{\text{O}}{\underset{\uparrow}{\text{S}}}-\text{OC}_2\text{H}_5$, ethyl ethanesulfinate; $\text{CH}_3-\overset{\text{O}}{\underset{\uparrow}{\text{S}}}-\text{CH}_2\text{COOH}$, methylsulfinylacetic acid. Such names must be interpreted with caution when they are found in the early literature because of the custom of naming sulfonium compounds as sulfoxines (see footnote on p. 867). Furthermore, some compounds reported to be sulfinic esters are actually sulfones.

more soluble members of the series may be isolated as their salts; ³⁸¹ the ferric salts are especially satisfactory for this purpose and have been used for the quantitative determination of sulfinic acids.

In the older literature ³⁸² the structure of the sulfinic acids was a subject of controversy. Some of the reactions mentioned below indicate the presence of an —OH group; others can best be explained by assuming that the hydrogen is attached to sulfur. From the viewpoint of modern theories of structure, no question of this sort need be raised. Considering the sulfinate anion, both oxygen and sulfur have unshared electron pairs and either atom may be involved in reactions.



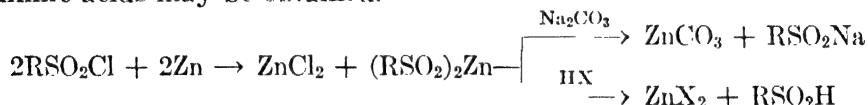
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The esters have the alkyl group attached to oxygen (RS—OR), as is shown by their resolution (p. 421).

Methods of Preparation

From Sulfonyl Chlorides. Reduction of sulfonyl chlorides by zinc dust in water gives zinc sulfates, from which sodium sulfates or free sulfinic acids may be obtained.



It has already been mentioned that sulfhydryl compounds may be obtained from reduction of sulfonyl chlorides by zinc and acids; this is a side reaction in the preparation of sulfates, but good yields of sulfates are usually obtained. ³⁸³ This method has been widely used in the aromatic series. It is apparently satisfactory for aliphatic compounds, but aliphatic sulfonyl chlorides have not been readily obtainable until recently (p. 889).

Of the other reducing agents used, sodium sulfite is probably the most satisfactory. ³⁸⁴



³⁸¹ Thomas, *J. Chem. Soc.*, **95**, 342 (1909); Krishna and Singh, *J. Am. Chem. Soc.*, **50**, 792 (1928); Meuwesen and Gebhardt, *Ber.*, **70**, 792 (1937).

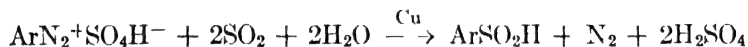
³⁸² For example, Otto and Rössing, *Ber.*, **25**, 230 (1892).

³⁸³ Hobson, *Ann.*, **102**, 73 (1857); *Ann.*, **106**, 287 (1858); Whitmore and Hamilton, *Org. Syntheses*, Coll. Vol. I, p. 479 (1932).

³⁸⁴ Smiles and Berc, *Org. Syntheses*, Coll. Vol. I, p. 7 (1932).

In the section dealing with thioisulfonic esters, reactions were noted in which sulfonyl halides were reduced to sulfinic acids (e.g., the reaction of sulfonyl chlorides with mercaptans [p. 907]). Some of the reactions of aryl esters of sulfonic acids gave similar results (p. 895). These are not important from a preparative standpoint, however.

From Diazonium Salts. A sulfinic acid is formed^{381, 385} when an acidic solution of a diazonium salt is saturated with sulfur dioxide, using copper powder as a catalyst.

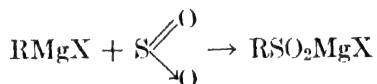


The yields are in some cases very good but appear to vary considerably with the structure of the diazonium compound.

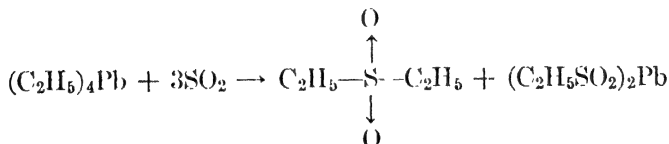
By the Friedel-Crafts Reaction. Aluminum chloride catalyzes the reaction of aromatic compounds with sulfur dioxide to give sulfinic acids.^{386, 387}



From Organometallic Compounds. Aliphatic, as well as aromatic, sulfinic acids may be prepared^{244, 388} by the reaction of the Grignard reagent with sulfur dioxide. The yields are generally rather low.



Zinc alkyls behave similarly.³⁸⁹ Tetracthyllead gives a sulfone and sulfinate.³⁸⁹



³⁸⁵ Gattermann, *Ber.*, **32**, 1136 (1899); Ger. pat. 130,119 [*Chem. Zentr.*, **1**, 959 (1902)]; Tröger and Hille, *J. prakt. Chem.*, [2] **68**, 297 (1903); *ibid.*, [2] **71**, 207 (1905); Todd and Shriner, *J. Am. Chem. Soc.*, **56**, 1382 (1934); Hann, *ibid.*, **57**, 2166 (1935); Sylvester and Wynne, *J. Chem. Soc.*, 691 (1936).

³⁸⁶ Friedel and Crafts, *Ann. chim. phys.*, [6] **14**, 442 (1888); Smiles and LeRossignol, *J. Chem. Soc.*, **93**, 745 (1903); Knoevenagel and Kenner, *Ber.*, **41**, 3315 (1908).

³⁸⁷ Kränzlein, "Aluminiumchlorid in der organischen Chemie," Verlag Chemie, G.M.B.H., Berlin (1932), 2nd Edn.

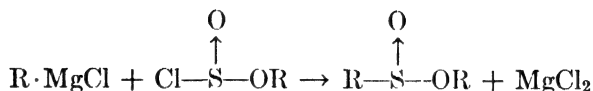
³⁸⁸ Rosenheim and Singer, *Ber.*, **37**, 2152 (1904).

³⁸⁹ Zuckschwerdt, *Ber.*, **7**, 292 (1874); Frankland and Lawrence, *J. Chem. Soc.*, **35**, 244 (1879).

Sulfonyl chloride reacts with the Grignard reagent,³⁹⁰ producing equivalent amounts of alkyl chloride and the sulfinic acid.

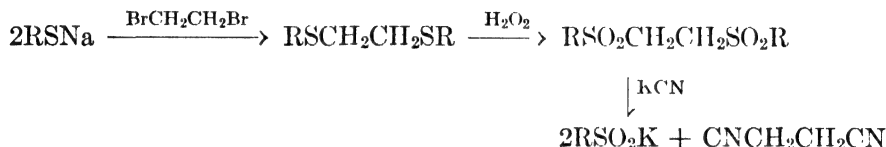


Alkyl chlorosulfites³⁹¹ react with the Grignard reagent to give alkyl esters of sulfinic acids (20–60 per cent).



The formation of sulfinic acids from the reactions of organometallic compounds with sulfonyl chlorides and with thiolsulfonic esters has already been discussed (pp. 899, 909). These are not generally used as preparative methods.

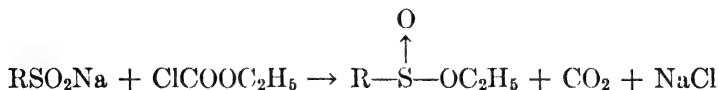
From Ethylene Disulfones. The cleavage of ethylene disulfones by potassium cyanide (p. 883) is an excellent method for the preparation of aliphatic sulfinates.



Although the same sequence of reactions can be used to obtain aromatic sulfinates, these are usually more readily available by other methods, and this synthesis is important for the aliphatic series only.

Other Methods. Sodium ethanesulfinate has been obtained³⁹² by the action of dry oxygen at 100–120° upon sodium ethylmercaptide, but the sulfinic acids are so readily oxidized that the oxidation of mercaptans is not a suitable method of preparation.

Formation of Acid Derivatives. It has been shown (p. 874) that the reactions of salts of sulfinic acids with alkyl halides give sulfones, not sulfinic esters. The esters* are formed,³⁹³ however, by the action of ethyl chlorocarbonate on the salts.



³⁹⁰ Oddo, *Gazz. chim. ital.*, **35**, II, 136 (1905); Raiford and Hazlett, *J. Am. Chem. Soc.*, **57**, 2172 (1935).

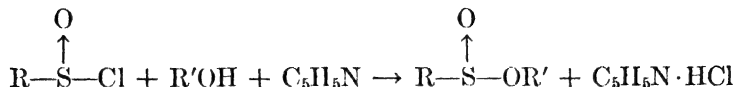
³⁹¹ Carré and Liebermann, *Compt. rend.*, **200**, 2086 (1935); *Bull. soc. chim.*, [5] **2**, 1700 (1935).

³⁹² Claesson, *J. prakt. Chem.*, [2] **15**, 222 (1877).

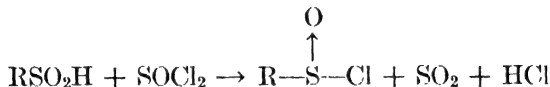
* Although isomeric, the sulfones and sulfinic esters differ considerably in their properties. For example, diethyl sulfone melts at 70° and boils at 248° while ethyl ethane sulfinate is a liquid, b.p. 60° (16 mm.)

³⁹³ Otto and Rössing, *J. prakt. Chem.*, [2] **47**, 152 (1893).

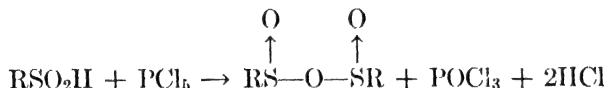
Esters are readily obtained ³⁹⁴ by the reaction of sulfinyl chlorides with alcohols in the presence of pyridine or potassium carbonate.



The sulfinyl chlorides are best prepared ³⁹⁵ by the reaction of the sulfinic acids with thionyl chloride in dry ether.



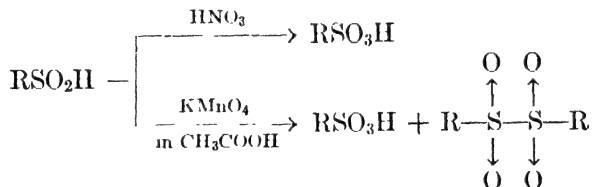
Anhydrides are formed ³⁹⁶ by the action of phosphorus pentachloride, phosgene, or acetic acid-sulfuric acid on sulfinic acids.



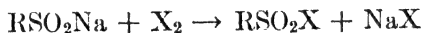
Sulfinamides may be prepared from the usual reaction of the acid chlorides with ammonia or amines.³⁹⁷

Reactions

Oxidation. Sulfinic acids are readily oxidized. They give sulfonic acids when treated with nitric acid,³⁹⁸ hydrogen peroxide,³⁹⁹ or potassium permanganate.²⁴¹ With permanganate in glacial acetic acid, α -disulfones are also formed (p. 884).



Sulfonyl halides are produced ^{398, 400} by the action of chlorine, bromine, or iodine (p. 907) on the salts of sulfinic acids.



³⁹⁴ Phillips, *J. Chem. Soc.*, **127**, 2553 (1925).

³⁹⁵ Hilditch and Smiles, *Ber.*, **41**, 4113 (1908).

³⁹⁶ Knoevenagel, Kenner, and Polack, *Ber.*, **41**, 3315, 3323 (1908); Otto, *Ber.*, **20**, 3337 (1887).

³⁹⁷ Heiduschka, *J. prakt. Chem.*, [2] **81**, 320 (1910); Hazlett and Raiford, *Proc. Iowa Acad. Sci.*, **42**, 120 (1935) [*C. A.*, **30**, 8185 (1936)].

³⁹⁸ Otto and Ostrop, *Ann.*, **141**, 370 (1867).

³⁹⁹ See Hann, Ref. 385.

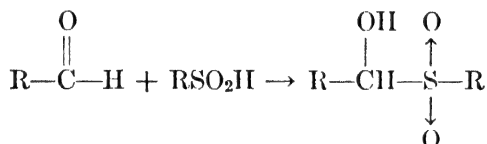
⁴⁰⁰ Otto, *Ann.*, **145**, 322 (1868).

The reaction of salts of sulfinic acids with "positive" halogen compounds also gives sulfonyl halides (p. 875), but under the conditions of the reactions the latter are usually converted to either sulfonic acids or disulfones.

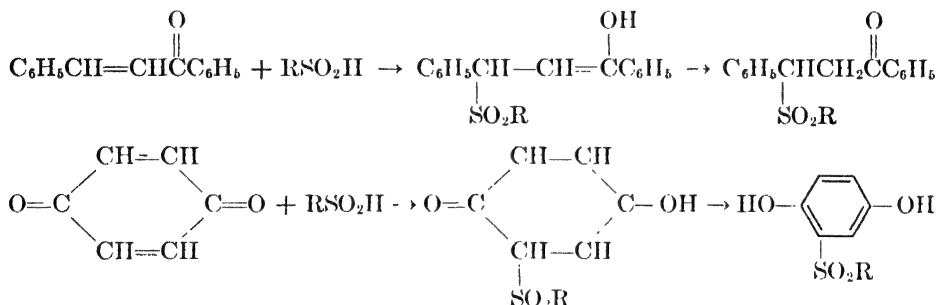
With Diazonium Salts. Sulfinic acids react with diazonium salts,⁴⁰¹ giving diazosulfones which may be decomposed to sulfones by heating.



With Aldehydes. Crystalline addition products are obtained from the reaction^{402, 403} of aldehydes with sulfinic acids. The products from aliphatic aldehydes are somewhat dissociated in solution but those from aromatic aldehydes are more stable.



With α,β -Unsaturated Ketones, Acids, etc. Sulfinic acids add, presumably by 1,4-addition, to conjugated systems such as chalcones,⁴⁰³ cinnamic acid,⁴⁰³ and quinones.⁴⁰⁴



Replacement by Metals. The reaction of aromatic sulfinic acids with mercuric chloride (or acetate) results in the elimination of the $-\text{SO}_2\text{H}$ group.⁴⁰⁵ This has been especially useful for obtaining aromatic mercurials of known orientation.



⁴⁰¹ Königs, *Ber.*, **10**, 1531 (1877); Bauer, *Ann.*, **229**, 353 (1885); Lamprecht, *Ber.*, **18**, 1468a (1885); v. Meyer, *J. prakt. Chem.*, [2] **56**, 272 (1897); Hantzsch, *Ber.*, **31**, 636 (1898); Troeger and Ewers, *J. prakt. Chem.*, [2] **62**, 369 (1900).

⁴⁰² v. Meyer, *J. prakt. Chem.*, [2] **63**, 167 (1901).

⁴⁰³ Kohler and Reimer, *Am. Chem. J.*, **31**, 163 (1904).

⁴⁰⁴ Hinsberg, *Ber.*, **27**, 3259 (1894); *Ber.*, **28**, 1315 (1895); Hinsberg and Himmelschein, *Ber.*, **29**, 2024 (1896).

⁴⁰⁵ Peters, *Ber.*, **38**, 2567 (1905); Kharasch and Chalkley, *J. Am. Chem. Soc.*, **43**, 611 (1921); Whitmore, Hamilton, and Thurman, *ibid.*, **45**, 1066 (1923); Coffey, *J. Chem. Soc.*, 637 (1926).

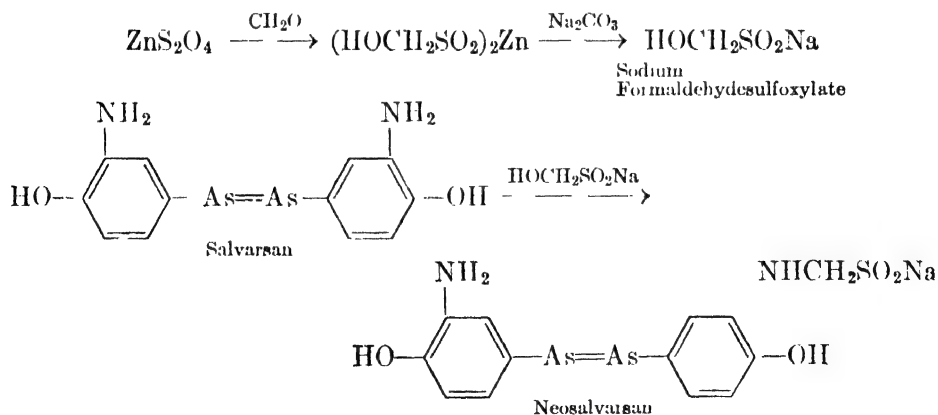
Camphor-10-sulfinic acid⁴⁰⁶ gives a similar reaction with arsenic trichloride.



Other Reactions. Sulfonyl interchange from the reaction of salts of sulfinic acids with thiolsulfonic esters and with certain sulfones has already been mentioned (pp. 911, 879). α -Disulfones are formed (p. 884) by the reaction of the salts with sulfonyl chlorides. The sulfinic acids are especially useful in preparing sulfones (p. 874). The disproportionation of free sulfinic acids (p. 906) to give sulfonic acids and thiolsulfonic esters and the reaction of the acids with phenylhydrazine (p. 906) have been noted. Sulfinic acids also react with hydroxylamine,⁴⁰⁷ with nitrous acid,⁴⁰⁸ and with nitroso compounds.⁴⁰⁹

Important Sulfinic Acids

The reaction of zinc dithionite (zinc hyposulfite) with formaldehyde, followed by treatment with sodium carbonate, gives sodium formaldehydesulfoxylate (also called "Rongalite C," "Sulfoxite C," and "Formopon"). The last is used as a reducing agent in vat dyeing and as a reagent for the introduction (upon nitrogen) of the $-\text{CH}_2\text{SO}_2\text{Na}$ group. Since that is a solubilizing group and is readily split off in the body, many medicinals are administered as their sulfoxylate derivatives; for example, neosalvarsan (neoarsphenamine), which is used in the treatment of syphilis, is much more soluble than salvarsan.



⁴⁰⁶ Loudon, *J. Chem. Soc.*, 391 (1937).

⁴⁰⁷ Whalen and Jones, *J. Am. Chem. Soc.*, **47**, 1353 (1925).

⁴⁰⁸ Koenigs, *Ber.*, **11**, 615 (1878).

⁴⁰⁹ Bamberger and Rising, *Ber.*, **34**, 228, 241 (1901).

XII. DERIVATIVES OF SULFENIC ACIDS

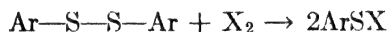
General Characteristics

Reactions from which sulfenic acids ($R-S-OH$) might be expected generally produce disulfides and thiolsulfonic esters.* However, the corresponding acid chlorides ($R-S-Cl$), amides ($R-S-NH_2$), esters ($R-S-OR$), and anhydrides ($R-S-O-S-R$) are known. Since sulfenyl halides are generally precursors of the others, it is convenient to study the entire class of derivatives of sulfenic acids by considering the methods of preparation and reactions of the halides.

The members of this series, as will be shown below, are more readily hydrolyzed than derivatives of sulfonic acids or sulfinic acids. The sulfenyl chlorides are extremely reactive. Only three aliphatic sulfenyl halides (Cl_3CSX , $(C_6H_5)_3CSX$, and $(CH_3)_3CSX$) are known;¹⁵⁰ none of these has hydrogen on the carbon atom which is attached to sulfur. The simple aromatic sulfenyl halides (C_6H_5SCl , $CH_3C_6H_4SCl$, etc.) react with moisture of the air and decompose rapidly; they are usually prepared immediately before use. Others (such as *p*-chloro-*o*-nitrophenylsulfenyl chloride) are more stable and may be stored for some time before appreciable decomposition occurs.

Preparation of Sulfenyl Halides

From Disulfides. Sulfenyl chlorides¹⁴⁹ and bromides¹⁵⁰ are probably most conveniently prepared by treatment of the disulfide with halogen under anhydrous conditions at low temperatures.



Aliphatic disulfides undergo chain halogenation¹⁵⁰ in preference to cleavage of the disulfide link; Cl_3CSCl and $(C_6H_5)_3CSCl$ are the only aliphatic sulfenyl chlorides which have been prepared by this method. Even tertiary butyl disulfide undergoes chain halogenation under these conditions.

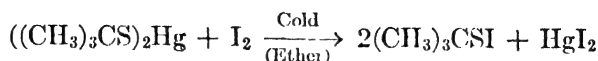
From Mercaptans. Under anhydrous conditions thiophenols react⁴¹⁰ with chlorine or bromine to give sulfenyl halides. In view of the ease of formation of disulfides from sulfhydryl compounds (p. 851), the former may be intermediates in this reaction.



* Apparently the only known acid of this series is α -anthraquinonesulfenic acid: Fries, *Ber.*, **45**, 2965 (1912); Fries and Schürmann, *Ber.*, **52**, 2182 (1919).

⁴¹⁰ Zincke, *Ber.*, **44**, 769 (1911).

Although the usual product from the reaction of a mercaptide with iodine is a disulfide (p. 861), the mercury salt of tertiary butyl mercaptan gives a sulfenyl iodide.⁴¹¹

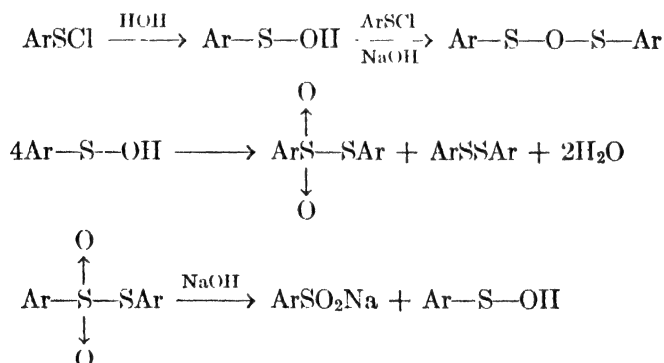


Sulfenyl thiocyanates, which may be prepared by the reaction of thiocyanogen⁴¹² with mercaptans, react similarly⁴¹² to the chlorides. Both aliphatic and aromatic sulfenyl thiocyanates have been prepared.

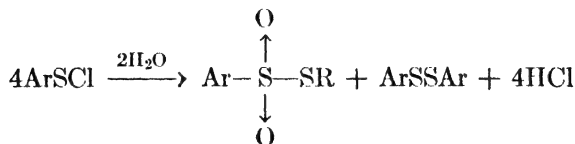


Reactions

Hydrolysis. Sulfenic anhydrides may be obtained^{347, 413} as initial products of the hydrolysis of sulfenyl chlorides. If the reaction is carried to completion in the presence of excess alkali the anhydrides are converted to disulfides and thiolsulfonic esters; the latter (*cf.* p. 909) are finally converted to disulfides and sulfinic acids. It is probable³⁴⁷ that sulfenic acids are intermediates in the hydrolysis both of sulfenyl chlorides and of thiolsulfonic esters.



The decomposition of sulfenyl chlorides in moist air or in boiling acetic acid⁴¹³ gives disulfides and thiolsulfonic esters.



⁴¹¹ Rheinboldt, *Rev. brasil. chim. São Paulo*, **4**, 169 (1937) [*C. A.*, **32**, 484 (1938)].

⁴¹² Lecher and Wittwer, *Ber.*, **55**, 1474 (1922); Lecher and Simon, *Ber.*, **54**, 632 (1921)

⁴¹³ Zincke and Eismayer, *Ber.*, **51**, 751 (1918).

The hydrolysis of sulfenic esters gives analogous results; by alkaline hydrolysis in aqueous solution ⁴¹² disulfides and sulfinic acids are formed; acetic acid ⁴¹⁴ produces disulfides and thiolsulfonic esters.

With Alcohols and Phenols. Sulfenyl chlorides react with alcohols ³⁴⁷ at room temperature to give disulfides and thiolsulfonic esters; at higher temperatures disulfides and sulfinic acids are produced. With phenols, nuclear substitution occurs.⁴¹⁵



Sodium alkoxides ⁴¹¹ and phenoxides ⁴¹⁶ may react with sulfenyl chlorides or sulfenyl thiocyanates ⁴¹² to produce sulfenyl esters.



It may be noted that the reaction of alkyl hypochlorites with mercaptides does not give sulfenic esters; disulfides are produced.



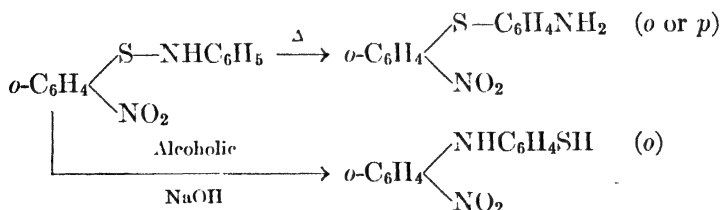
Formation of Sulfenamides. Sulfenyl halides react with ammonia,⁴¹³ primary amines, and secondary amines ^{417, 418} to give sulfenamides.



When the reaction is carried out in ether the hydrochloride of the sulfenamide is obtained. The hydrochlorides and the free sulfenamides have been used ⁴¹⁷ as solid derivatives of amines. The original amine is readily recovered ⁴¹⁷ from the amide.



Sulfenanilides undergo rearrangement ⁴¹⁸ to sulfides when heated. If alcoholic alkali is used the rearrangement gives a diaryl amine.



⁴¹⁴ Fries and Schurmann, *Ber.*, **52**, 2182 (1919).

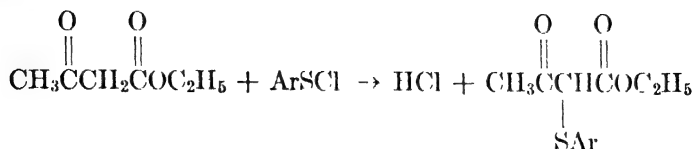
⁴¹⁵ Foss, Stehle, Shusett, and Hadburg, *J. Am. Chem. Soc.*, **60**, 2729 (1938).

⁴¹⁶ Learmouth and Smiles, *J. Chem. Soc.*, 327 (1936).

⁴¹⁷ Billman and O'Mahoney, *J. Am. Chem. Soc.*, **61**, 2340 (1939).

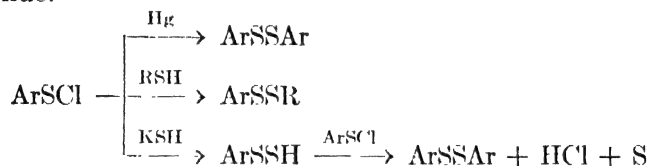
⁴¹⁸ Moore and Johnson, *ibid.*, **57**, 1517 (1935); *ibid.*, **58**, 1091, 1960 (1936).

With Active Methylene Compounds. Good yields of substitution products may sometimes be obtained by the reaction of sulfenyl chlorides with active methylene compounds.^{413, 419}

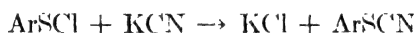


The reaction does not always proceed smoothly; sometimes disulfides or tars are formed. However, acetophenone and acetone, which are generally considered to be rather unreactive methylene compounds, react satisfactorily. The same product is formed from the copper salt of acetoacetic ester⁴¹⁹ as from the ester.

Other Reactions. Sulfenyl halides appear to be able to add to the olefinic double bond (p. 856). Disulfides are formed by the reactions of sulfenyl halides with metals,⁴¹¹ sulfhydryl compounds,⁴¹¹ or potassium hydrosulfide.⁴²⁰



Thiocyanates are formed⁴¹³ by the action of potassium cyanide.



The use of sulfenyl halides in the synthesis of thiolsulfonic esters has already been discussed (p. 906).

XIII. THIOALDEHYDES AND THIOKETONES*

General Characteristics

One of the most outstanding differences between carbonyl compounds and their thio analogs is the tendency of the thio compounds to undergo polymerization. Thioketones, in contrast to ketones, readily form dimers⁴²¹ and cyclic trimers; the isolation of monomers is often difficult. The thioaldehydes polymerize still more readily than the thioketones;

⁴¹⁹ Zincke and Baeumer, *Ann.*, **416**, 86 (1918).

⁴²⁰ Dougherty and Haas, *J. Am. Chem. Soc.*, **59**, 2469 (1937).

* Schönberg, "Thioketone, Thioacetale und Aethylen Sulfide," *Ahrens Sammlung Chemischer und chemisch-technischer Vorträge*, Neue Folge, Heft 19, Enke, Stuttgart (1933).

⁴²¹ Kretov and Komissarov, *J. Gen. Chem. (U.S.S.R.)*, **5**, 388 (1935) [*C. A.*, **29**, 6207 (1935)].

monomeric thioformaldehyde and thioacetaldehyde have not been obtained except (possibly) in solution. The compounds (e.g., 9-thiophenanthraldehyde⁴²²) of high molecular weight may be obtained as monomers.

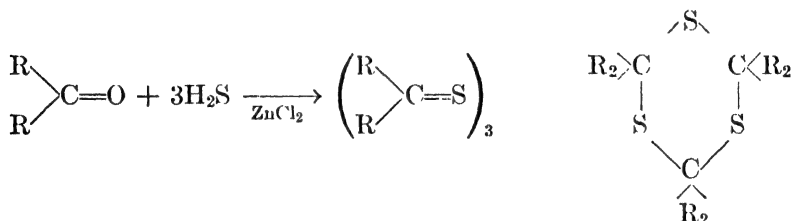
Although the >C=O group is not a chromophore unless it is conjugated with another unsaturated group, the unconjugated >C=S group is a potent chromophore. The monomeric thioaldehydes and thioketones are blue, their polymers colorless.

The monomeric thioaldehydes and thioketones of low molecular weight have very disagreeable odors.*

Thioacetals have been discussed earlier (p. 849).

Preparation

Aldehydes and Ketones with Hydrogen Sulfide. Aldehydes react with hydrogen sulfide in the absence of a catalyst,⁴²³ but results are generally more satisfactory if acid or zinc chloride is used. These catalysts are necessary⁴²³ for the reaction of ketones with hydrogen sulfide. Aliphatic⁴²³ and aromatic⁴²⁴ aldehydes, dialkyl ketones,^{423, 425} aryl alkyl ketones,⁴²³ and diaryl ketones⁴²⁶ all undergo this reaction.



Sodium thiosulfate may be used in place of hydrogen sulfide in this reaction.⁴²⁷ Both the *cis* and *trans* forms of trithioaldehydes (three hydrogens on the same side of the plane of the ring or two hydrogens and an alkyl group on the same side) may be isolated.^{424, 428} The lower-melting

⁴²² Wood and Bost, *J. Am. Chem. Soc.*, **59**, 1721 (1937).

* Thioisobutyraldehyde [Pfeiffer, *Ber.*, **5**, 699 (1872)] is said to have an "abominable alliaceous odor" and thioisovaleraldehyde [Schroeder, *Ber.*, **4**, 400 (1871)] to have an "offensive and persistent odor." Monomeric thioacetone [Fromm and Baumann, *Ber.*, **22**, 1035 (1889)] "has an offensive nauseating odor, much worse than that of other volatile sulfur compounds"; its preparation "caused disturbances in the neighboring streets in Freiburg and precipitated a storm of protests" and "extremely minute amounts make millions of cubic meters of air repulsive."

⁴²³ Baumann and Fromm, *Ber.*, **28**, 895 (1895).

⁴²⁴ Baumann and Fromm, *Ber.*, **24**, 1421, 3591 (1891).

⁴²⁵ Fromm and Baumann, *Ber.*, **22**, 1035, 2595 (1889); Peters, *Ber.*, **40**, 1480 (1907).

⁴²⁶ Bost and Cosby, *J. Am. Chem. Soc.*, **57**, 1404 (1935).

⁴²⁷ Anino, *J. prakt. Chem.*, **77**, 367 (1908); *Ber.*, **35**, 3251 (1902).

⁴²⁸ Fromm, *Ber.*, **32**, 2650 (1899); Müller and Schiller, *J. prakt. Chem.*, **116**, 175 (1927);

d Soffner, *Ber.*, **57**, 371 (1924); Fromm and Schultis, *Ber.*, **56**, 937 (1923).

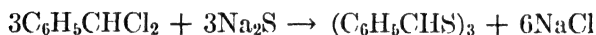
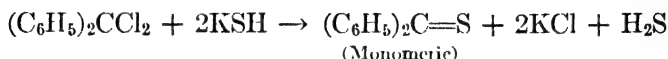
The reaction of formaldehyde with hydrogen sulfide has been studied ^{424, 430} by a number of investigators. Methylation of the reaction mixture gives $\text{CH}_2(\text{SCH}_3)_2$ and $\text{CH}_3\text{SCH}_2\text{SCH}_2\text{SCH}_3$ (showing the presence of $\text{CH}_2(\text{SH})_2$ and $\text{HSCH}_2\text{SCH}_2\text{SH}$), and treatment with iodine gives a cyclic disulfide, $\text{CH}_2-\text{S}-\text{CH}_2-\text{S}-\text{CH}_2-\text{S}-\text{S}$, derived from

$$\begin{array}{c} \text{H}_2\text{C=O} + \text{H}_2\text{S} \rightleftharpoons \text{H}_2\text{C} \begin{matrix} \nearrow \text{SH} \\ \searrow \text{OH} \end{matrix} \rightleftharpoons \text{H}_2\text{O} + \text{H}_2\text{C=S} \\ \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \downarrow \xrightarrow{\text{H}_2\text{S}} \\ \text{etc. } \rightleftharpoons \text{HSCH}_2\text{SCH}_2\text{SH} \xleftarrow{\text{CH}_2\text{O}} \text{H}_2\text{C} \begin{matrix} \nearrow \text{SH} \\ \searrow \text{SH} \end{matrix} \end{array}$$
$$(\text{CH}_3\text{CH}(\text{OH})\text{NH}_2)_3 \xrightarrow{\text{H}_2\text{S}} \begin{array}{c} \text{CH}_3 \\ | \\ \text{S}-\text{CH} \\ / \quad \backslash \\ \text{CH}_3\text{CH} \quad \text{NH}\cdot\text{HCNS} \\ \backslash \quad / \\ \text{S}-\text{CH} \\ | \\ \text{CH}_3 \end{array} \xrightarrow{(\text{HOH})} (\text{CH}_3\text{CHS})_3$$
$$\text{RCH=NNHC}_6\text{H}_3(\text{NO}_2)_2 \xrightarrow[\text{(H}_2\text{SO}_4\text{)}]{\text{H}_2\text{S}} \text{RCHS} + (\text{O}_2\text{N})_2\text{C}_6\text{H}_3\text{NHNH}_2 \cdot \text{H}_2\text{SO}_4$$

⁴³¹ Wohl, *Ber.*, **19**, 2344 (1886).

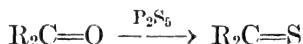
The reactions of polyfunctional carbonyl compounds with hydrogen sulfide are sometimes different from the simple members of the series; for example, thiophenes have been obtained⁴³² from 1,4-diketones.

From Methylene Halides and Metal Sulfides. Compounds with two halogens attached to the same carbon atom may be converted to thioaldehydes or thioketones by the action⁴³³ of sodium (or potassium) hydrosulfides or sulfides.

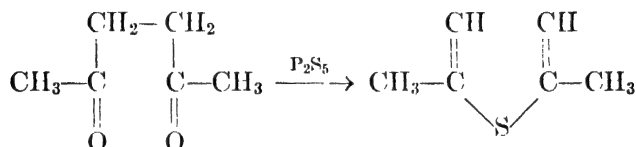


In preparing thioaldehydes by this method⁴³⁴ the Cannizzaro reaction (see below) is responsible for the formation of by-products.

From Ketones and Phosphorus Pentasulfide. Most of the products obtained^{421, 435} from the reaction of ketones with phosphorus pentasulfide are dimeric but a few are monomeric.



When 1,4-diketones are used thiophenes are formed.⁴³⁶



Other Methods. It has been noted (p. 862) that disulfides are produced by the reaction of ketones with ammonium hydrosulfide; the reaction is a complex one,⁴³⁷ however, and it appears that thioketones are intermediates. Methylene halides react⁴³⁸ with thioacetic acid or its salts to give thioketones.



α,α -Dichlorodiethyl sulfide is converted to trithioacetaldehyde by the action of silver sulfide, silver oxide, hydrogen sulfide, or sodium hy-

⁴³² Mitra, *J. Indian Chem. Soc.*, **15**, 59 (1938) [*C. A.*, **32**, 4982 (1938)].

⁴³³ Behr, *Ber.*, **5**, 970 (1872); Klinger, *Ber.*, **15**, 861 (1882); Gattermann and Schulze, *Ber.*, **29**, 2944 (1896); Staudinger and Freudenberg, *Org. Syntheses*, **11**, 94 (1931).

⁴³⁴ Wood and Bost, *J. Am. Chem. Soc.*, **59**, 1011 (1937).

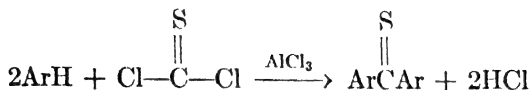
⁴³⁵ Spring, *Bull. soc. chim.*, [2] **40**, 66 (1883).

⁴³⁶ Paal, *Ber.*, **18**, 367, 2251 (1885).

⁴³⁷ Willegerodt, *Ber.*, **20**, 2467 (1887); Baumann and Fromm, *Ber.*, **28**, 907 (1895); Manchot and Krische, *Ann.*, **337**, 170 (1904); Fromm and Holler, *Ber.*, **40**, 2978 (1907).

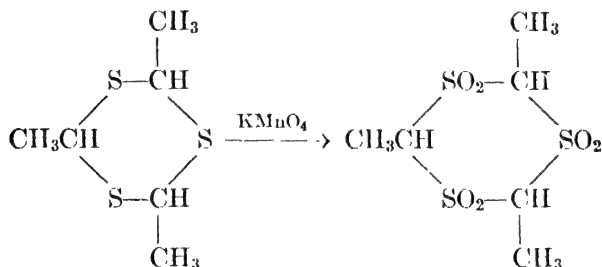
⁴³⁸ Spring, *Ber.*, **14**, 758 (1881); Schönberg, Schutz, and Nickel, *Ber.*, **61**, 1375 (1928) Kitamura, *J. Pharm. Soc. Japan*, **57**, 893 (1937) [*C. A.*, **32**, 1680 (1938)].

droxide.⁴³⁹ Thioacrolein is formed⁴⁴⁰ by heating glycerol with sulfur at 175–200° under slightly elevated pressures. Diarylthioketones may be prepared⁴⁴¹ by the Friedel-Crafts reaction, using thiophosgene.



Reactions

Oxidation. Oxidation of the cyclic trimers may be carried out in the same way as the oxidation of ordinary sulfides (p. 874). The cyclic trisulfones⁴⁴² obtained from trithioaldehydes in this way form salts when treated with sodium ethoxide, may be alkylated, and have the general properties of methylene disulfones (p. 881).



It is interesting to note that, while the *cis* and *trans* isomers of the trithioaldehydes might be expected to give *cis* and *trans* sulfones, only one trisulfone may be obtained. This may be attributed to the labilizing influence of the sulfone group upon hydrogen, allowing the formation of

an anion $\left(\begin{array}{c} \text{CH}_3 \\ | \\ -\text{SO}_2\text{CHSO}_2- \end{array} \rightleftharpoons \text{H}^+ + \left[\begin{array}{c} \text{CH}_3 \\ | \\ -\text{SO}_2\text{CSO}_2- \end{array} \right]^- \right)$ which may readily change from one geometric form to the other.

The trisulfoxide from trithioformaldehyde may be obtained⁴⁴³ in both *cis* and *trans* forms (p. 484).

Though most of the monomeric thioketones are converted^{426, 438} to ketones by the action of hydrogen peroxide, some of the complex ones fail to react. Oxidation of trithioformaldehyde by aqueous chlorine has been discussed elsewhere (p. 858).

⁴³⁹ Mann and Pope, *J. Chem. Soc.*, **123**, 1178 (1923).

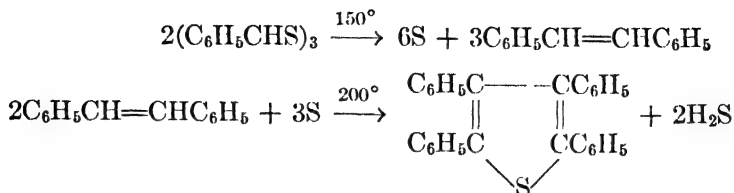
⁴⁴⁰ Delson, U. S. pat. 2,067,261 [C. A., **31**, 1555 (1937)].

⁴⁴¹ Gattermann, *Ber.*, **28**, 2869 (1895).

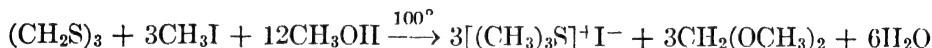
⁴⁴² Baumann and Fromm, *Ber.*, **22**, 2606 (1889); Baumann and Camps, *Ber.*, **23**, 69, 1874 (1890); Camps, *Ber.*, **25**, 234, 248 (1892); Baumann, *Ber.*, **26**, 2074 (1893); Lomnitz, *Ber.*, **27**, 1667 (1894); Peters, *Ber.*, **38**, 2566 (1905).

⁴⁴³ Hinsberg, *J. prakt. Chem.*, [2] **85**, 337 (1912); *ibid.*, **142**, 135 (1935). See also the reference on p. 484.

Pyrolysis. Olefins and thiophene derivatives are formed ⁴⁴⁴ by heating thioaldehydes or thioketones. For example, stilbene ⁴²⁶ or thionessal ⁴⁴⁴ (tetraphenylthiophene) may be obtained from trithiobenzaldehyde.



With Alkyl Iodides. Thioaldehydes and thioketones react ⁴⁴⁵ with alkyl iodides (less readily, with alkyl bromides), forming sulfonium salts.



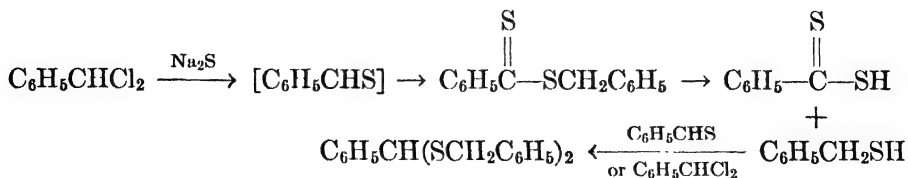
The products appear to be those which might be expected by assuming that the trithioaldehyde behaves like an ordinary sulfide, giving a sulfonium salt which undergoes alkyl interchange according to the reaction already noted (p. 868).

With Salts of Heavy Metals. The monomeric, dimeric, and trimeric thioaldehydes and thioketones resemble the sulfides (p. 858) in their ability ^{421, 426} to form addition products with the salts of heavy metals such as mercury, platinum, and silver. Both geometric isomers of tri-thioacetaldehyde, for example, give salts with silver nitrate with the composition $(\text{CH}_3\text{CHS})_3 \cdot \text{AgNO}_3$ and $(\text{CH}_3\text{CHS})_3 \cdot 3\text{AgNO}_3$.

Other Reactions. Thioketones are hydrolyzed ⁴²⁶ to ketones by heating with dilute alkali.



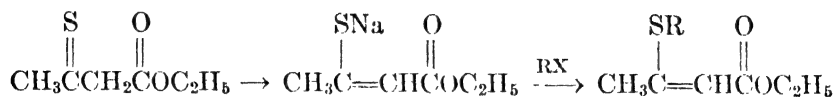
The isolation ⁴³⁴ of benzyl dithiobenzoate, dithiobenzoic acid, and benzyl mercaptan from the reaction of benzal chloride with sodium sulfide shows that thioaldehydes of the aromatic series may undergo auto-oxidation-reduction in the same way as their oxygen analogs.



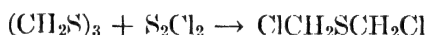
⁴⁴⁴ Kopp, *Ber.*, **25**, 600 (1892); *Ann.*, **277**, 339 (1893); Baumann and Klett, *Ber.*, **24**, 3307 (1891). See also Behr, *Ref.* 433, and Baumann and Fromm, *Ref.* 424.

⁴⁴⁵ Reychler, *Bull. soc. chim.*, [3] **33**, 1226 (1905); Platanov and Anismov, *J. Gen. Chem (U.S.S.R.)*, **5**, 622 (1935) [*C. A.*, **29**, 7277 (1935)].

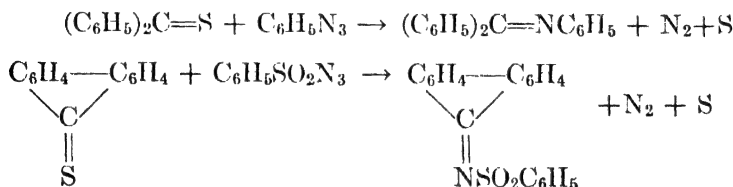
Thioketones react with carbonyl reagents; thiobenzophenone, for example,⁴³³ gives benzophenoneoxime when treated with hydroxylamine. β -Thioketonic esters, prepared⁴⁴⁶ by reaction of a β -keto ester with hydrogen sulfide, form sodio derivatives but upon treatment with an alkyl halide undergo alkylation on sulfur, rather than on carbon as is usual with their oxygen analogs.



Trithioformaldehyde is cleaved⁴³⁹ by treatment with sulfur chloride.



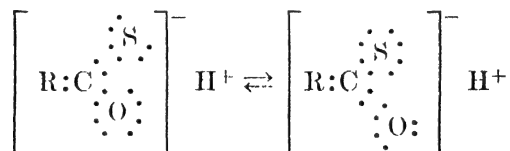
Anils are formed⁴⁴⁷ by the reaction of thioketones with azides.



XIV. THIO ACIDS AND THEIR DERIVATIVES

General Characteristics

The monothio analogs of the carboxylic acids exist in only one form. By analogy with the carboxylic acids, their structure may be a resonance hybrid of the thiol and thion structures.



In most of the reactions of thio acids and their salts the result is that expected from the presence of a —SH group, and there are arguments⁴⁴⁸ for considering this the favored structure.

The acids have disagreeable odors and are slowly decomposed upon exposure to air. Thioformic acid is not stable but loses hydrogen sulfide and forms an amorphous solid mass.⁴⁴⁹ Thio acids are less associated

⁴⁴⁶ Mitra, *J. Indian Chem. Soc.*, **15**, 31 (1938) [*C. A.*, **32**, 4945 (1938)].

⁴⁴⁷ Schönberg and Urban, *J. Chem. Soc.*, 530 (1935).

⁴⁴⁸ Bloch, *Compt. rend.*, **206**, 679 (1938).

⁴⁴⁹ Auger, *ibid.*, **139**, 798 (1904).

(compare ROH and RSH, p. 840), and the lower members of the series have lower boiling points than the carboxylic acids.

The alkali metal salts of the thio acids are crystalline, water-soluble compounds, but the heavy metal salts are generally insoluble in water and decompose rapidly ⁴⁵⁰ with precipitation of the metal sulfide.

Very few aliphatic dithio acids (RCS₂H) are known, but several of the aromatic series have been prepared. They oxidize readily and are extremely difficult to handle.

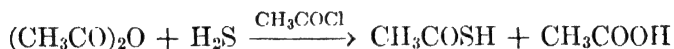
Thiol esters $\left(\text{R}-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{SR} \end{array} \right)$, thion esters $\left(\text{R}-\text{C} \begin{array}{l} \nearrow \text{S} \\ \searrow \text{OR} \end{array} \right)$, and dithio esters $\left(\text{R}-\text{C} \begin{array}{l} \nearrow \text{S} \\ \searrow \text{SR} \end{array} \right)$ are known. Some thion and thiol esters may be interconverted by heating.⁴⁵¹ The thion esters of low molecular weight are oxyluminescent.

The prefixes thiol and thion are used only in the nomenclature of the esters, since the only possible thioamides and thio acid chlorides are those corresponding to the thion esters; those corresponding to the thiol esters are the same as the amides and acid chlorides of carboxylic acids.

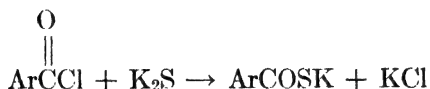
The thio derivatives of carbonic acids may have distinctive structures and reactions and will therefore be discussed separately in the concluding portion of this chapter.

Preparation

Preparation of Thio Acids. A good yield of thioacetic acid is obtained ⁴⁵² by passing hydrogen sulfide into a mixture of acetic anhydride and acetyl chloride.



Aromatic acid chlorides react with aqueous potassium hydrosulfide ⁴⁵³ or sulfide ⁴⁵⁴ to give thio acids, but aliphatic acid chlorides are too readily hydrolyzed to give satisfactory results.



⁴⁵⁰ Tarugi, *Gazz. chim. ital.*, **27**, 11, 153 (1897).

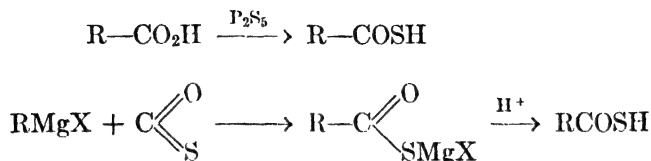
⁴⁵¹ Wheeler and Barnes, *Am. Chem. J.*, **22**, 141 (1899); *ibid.*, **24**, 60 (1900); Schönberg *et al.*, *Ber.*, **63**, 178 (1930); Karjala and McElvain, *J. Am. Chem. Soc.*, **55**, 2966 (1933); Schönberg *et al.*, *Ber.*, **64**, 1390, 2582 (1931); *Ber.*, **65**, 289 (1932); *Ann.*, **483**, 107 (1930).

⁴⁵² Clarke and Hartman, *J. Am. Chem. Soc.*, **46**, 1731 (1924).

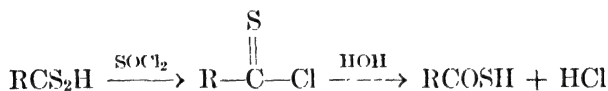
⁴⁵³ Jacquemin and Vosselmann, *Compt. rend.*, **49**, 371 (1859); Auger and Biley, *ibid.*, **136**, 555 (1903).

⁴⁵⁴ Cloez, *Ann.*, **115**, 27 (1860). See also Klinger, *Ref.* 433.

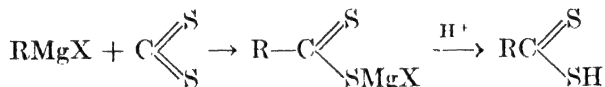
Thio acids have also been obtained from the reaction of carboxylic acids with phosphorus pentasulfide ⁴⁵⁵ and from the reaction of carbon oxysulfide with the Grignard reagent. ⁴⁵⁶



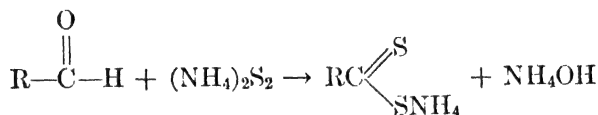
They have also been prepared ⁴⁵⁷ from dithio acids by formation of thio acid chlorides, followed by hydrolysis.



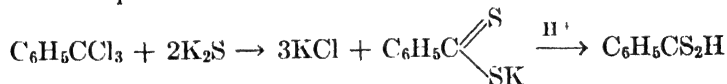
Preparation of Dithio Acids. Probably the most common method of preparation of dithio acids is the reaction ^{457, 458} of a Grignard reagent with carbon disulfide.



Aldehydes are converted ⁴⁵⁹ to dithio acids by treatment with ammonium polysulfide.



Dithiobenzoic acid ⁴⁶⁰ is readily obtained by the reaction of benzo-trichloride with potassium sulfide.



⁴⁵⁵ Kekulé, *Ann.*, **90**, 309 (1854); Schiff, *Ber.*, **28**, 1204 (1895).

⁴⁵⁶ Weigert, *Ber.*, **36**, 1007 (1903).

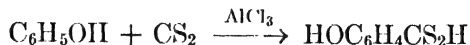
⁴⁵⁷ Bloch, *Compt. rend.*, **204**, 1342 (1937).

⁴⁵⁸ Houben and Schulze, *Ber.*, **43**, 2481 (1910); *Ber.*, **44**, 3235 (1911).

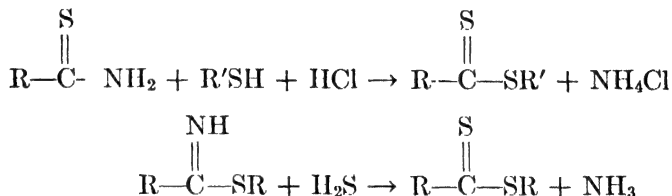
⁴⁵⁹ Bruni and Levi, *Atti. accad. Lincei*, **32**, i, 5 (1923) [*C. A.*, **18**, 2693 (1924)]; Bloch, Höhn, and Bugge, *J. prakt. Chem.*, **82**, 473 (1910).

⁴⁶⁰ Staudinger and Siegwart, *Helv. Chim. Acta*, **3**, 824 (1920). For a similar reaction using chloroform, see Nicol, *Proc. Roy. Soc. Edinburgh*, **10**, 425 (1882); *J. Chem. Soc.*, **42**, 589 (1882); Delmont, *J. pharm. chim.*, [5] **24**, 425 (1892); *J. Chem. Soc.*, **62**, 421 (1892); Levi, *Atti accad. Lincei*, [6] **9**, 170 (1929) [*C. A.*, **23**, 3438 (1929)].

Aromatic dithio acids have been obtained⁴⁶¹ by the reaction of phenols with carbon disulfide in the presence of aluminum chloride.

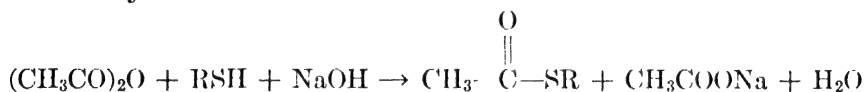


Preparation of Dithio Esters. Esters of the dithio acids have been prepared by the action of mercaptans on thioamides in the presence of hydrogen chloride⁴⁶² and by the action of hydrogen sulfide on imino thio esters⁷⁴ (p. 851).

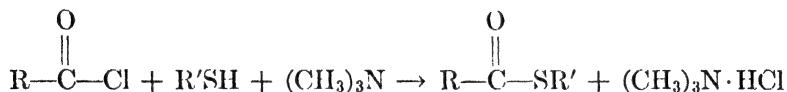


The *ortho* esters of this series have been mentioned previously (p. 848).

Preparation of Thiol Esters. The formation of thiol esters by the reaction of carboxylic acids with sulfhydryl compounds has been discussed (p. 848). Mercaptans may be acetylated⁴⁶³ with acetic anhydride and aqueous sodium hydroxide; with mercaptans of high molecular weight better yields⁴⁶³ are obtained by using sodium acetate in place of sodium hydroxide.



Aromatic acid chlorides also give satisfactory results with mercaptans and aqueous alkali. Aliphatic acid chlorides are too readily hydrolyzed to be used in aqueous solution but react under anhydrous conditions with thiophenols⁴⁶⁴ and mercaptans. Pyridine⁴⁶⁵ or trimethylamine⁴⁶⁶ appears to cause the acylation to occur more smoothly.



Thiol esters have also been obtained by the reaction of acyl halides with mercaptides,⁴⁶⁷ by alkylation of the salts of thio acids,⁴⁴⁸ by the

⁴⁶¹ Jörg, *Ber.*, **60**, 1466 (1927).

⁴⁶² Reid, *Orig. Com. 8th Intern. Congr. Appl. Chem.* (Appendix), **25**, 423 (1912) [*C. A.*, **7**, 2190 (1913)].

⁴⁶³ Wenzel and Reid, *J. Am. Chem. Soc.*, **59**, 1089 (1937).

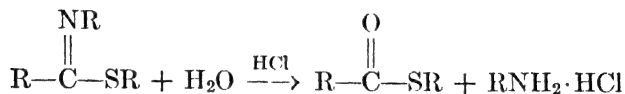
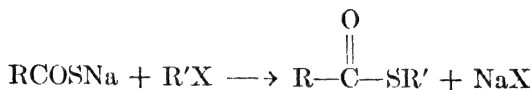
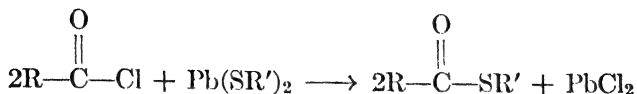
⁴⁶⁴ Michler, *Ber.*, **7**, 1312 (1874), Jones and Tasker, *J. Chem. Soc.*, **95**, 1904 (1909).

⁴⁶⁵ Holmberg, *Arkiv. Kemi, Mineral. Geol.*, **12B**, No. 47 (1938) [*C. A.*, **32**, 4151 (1938)].

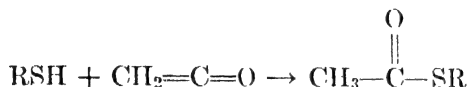
⁴⁶⁶ Ralston, Segebrecht, and Bauer, *J. Org. Chem.*, **4**, 503 (1939).

⁴⁶⁷ Michler, *Ann.*, **176**, 182 (1875); Obermayer, *Ber.*, **20**, 2920 (1887).

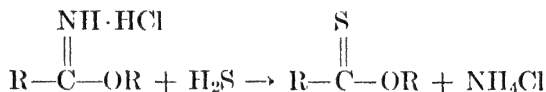
hydrolysis of imino thio esters,⁴⁶⁸ and by the action of mercaptides on esters.⁴⁶⁹



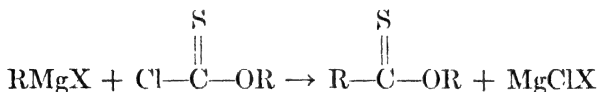
Ketene⁴⁷⁰ reacts readily with mercaptans, giving high yields of thiol esters.



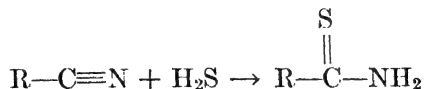
Preparation of Thion Esters. The method ordinarily used^{451, 471} for the preparation of thion esters is the reaction of dry hydrogen sulfide with imino esters.



Thion esters have also been obtained⁴⁷² from the reaction of the Grignard reagent with chlorothioncarbonates.



Preparation of Thioamides. Thioamides are usually prepared by the addition of hydrogen sulfide to a nitrile.⁴⁷³



⁴⁶⁸ Wallach and Bleibtreu, *Ber.*, **12**, 1062 (1879).

⁴⁶⁹ Seifert, *J. prakt. Chem.*, [2] **31**, 462 (1885).

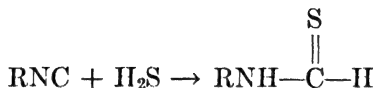
⁴⁷⁰ Hurd and Williams, *J. Am. Chem. Soc.*, **58**, 962 (1936).

⁴⁷¹ Sakurada, *Mem. Coll. Sci. Kyoto*, **9**, 237 (1926); *ibid.*, **10**, 79 (1926) [*C. A.*, **21**, 2458 3609 (1927)].

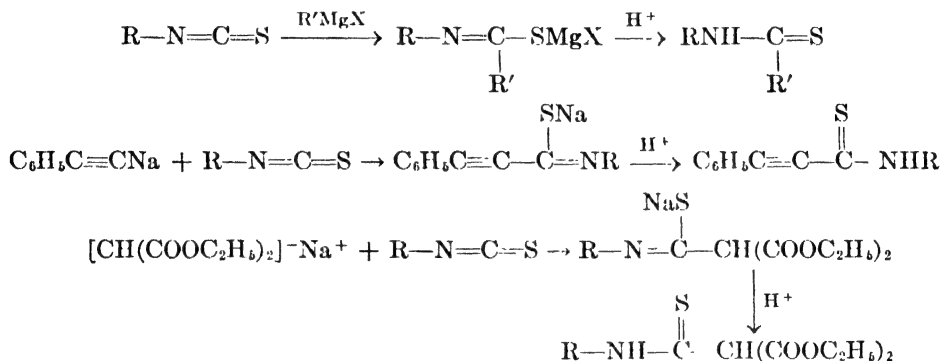
⁴⁷² Delepine, *Bull. soc. chim.*, [4] **49**, 904 (1911).

⁴⁷³ Gautier, *Ann.*, **142**, 289 (1867); Ralston, van der Wal, and McCorkle, *J. Org. Chem.*, **4**, 68 (1939).

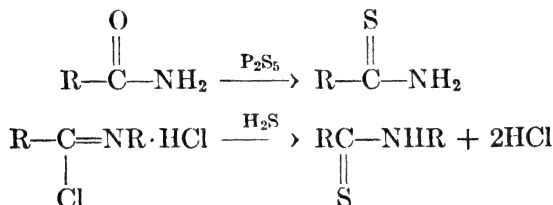
The reaction is carried out in a sealed tube or by adding the nitrile to alcohol that has been saturated with ammonia and then with hydrogen sulfide. In the case of certain nitriles which do not react under these conditions, high yields of thioamides have been obtained ⁴⁷⁴ by replacing the ammonia with triethanolamine. Isonitriles react with hydrogen sulfide to give thioformamides. ^{475, 476}



The reactions of isothiocyanates with the Grignard reagent, ⁴⁷⁷ sodium phenylacetylide, ⁴⁷⁸ or the sodium derivative of active methylene compounds ⁴⁷⁹ may be used for the preparation of thioamides.



Thioamides have also been prepared by the reaction of amides with phosphorus pentasulfide, ^{476, 480} from iminochlorides, ⁴⁸¹ from amidines, ^{480, 482} and by the Friedel-Crafts reaction. ⁴⁸³



⁴⁷⁴ Olin and Johnson, *Rec. trav. chim.*, **50**, 72 (1931).

⁴⁷⁵ Hofmann, *Ber.*, **10**, 1095 (1877).

⁴⁷⁶ Hofmann, *Ber.*, **11**, 338 (1878).

⁴⁷⁷ Sachs and Loevy, *Ber.*, **37**, 874 (1904); Gilman and Furry, *J. Am. Chem. Soc.*, **50**, 1214 (1928); Schwartz and Johnson, *ibid.*, **53**, 1063 (1931).

⁴⁷⁸ Worrall, *J. Am. Chem. Soc.*, **59**, 1486 (1937).

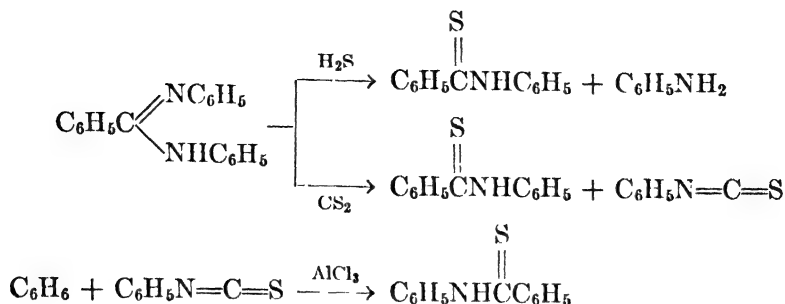
⁴⁷⁹ Ruhemann, *J. Chem. Soc.*, **93**, 621, 625 (1908); Worrall, *J. Am. Chem. Soc.*, **50**, 1457 (1928).

⁴⁸⁰ Berntsen, *Ber.*, **11**, 503 (1878).

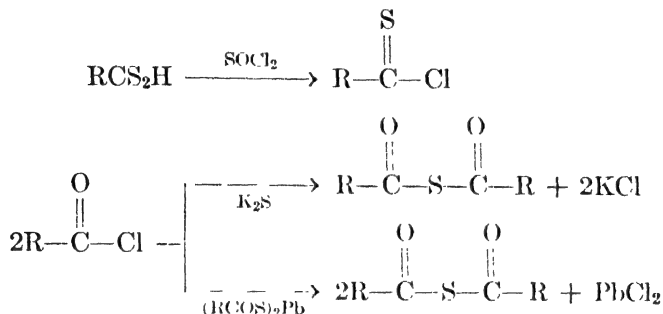
⁴⁸¹ Leo, *Ber.*, **10**, 2134 (1877).

⁴⁸² Berntsen, *Ber.*, **10**, 1238 (1877); *Ann.*, **192**, 29 (1878).

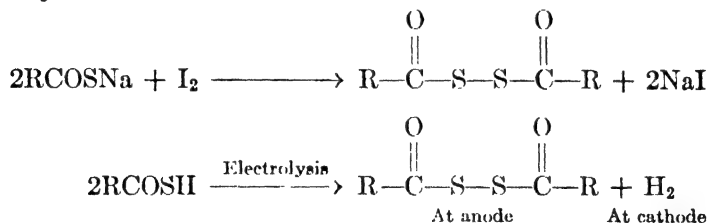
⁴⁸³ Friedmann and Gattermann, *Ber.*, **25**, 3525 (1892).



Preparation of Thio Acid Chlorides and Anhydrides. Thio acid chlorides are prepared ^{457, 484} by the reaction of dithio acids with thionyl chloride. Thio anhydrides (diacyl sulfides) are obtained ^{147, 485} by the reaction of an acid chloride with potassium sulfide or with the lead salt of a thio acid.



Diacyl disulfides may be obtained by the method already mentioned (p. 862), by the reaction of iodine with sodium salts of thio acids,⁴⁴⁸ or by the electrolysis of thio acids.⁴⁸⁶



Reactions

Reactions of Thio Acids. Probably the most notable characteristic of thio acids is their reactivity as acylating agents. Thioacetic acid, for example, acetylates amines⁴⁸⁷ readily at room temperature. Thio acids

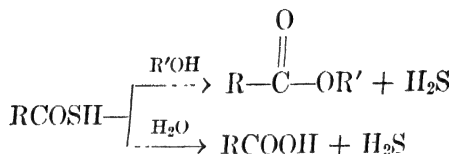
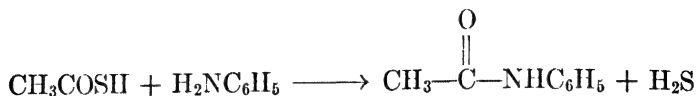
⁴⁸⁴ Staudinger and Siegwart, Ref. 460.

⁴⁸⁵ Davies, *Ber.*, **24**, 3549, 4251 (1891); Fromm, *Ann.*, **348**, 144 (1906).

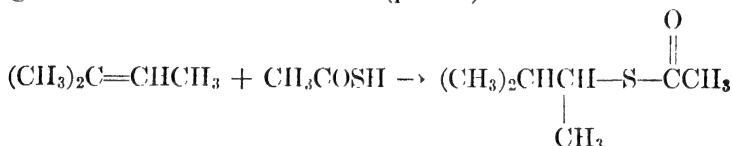
⁴⁸⁶ Bunge, *Ber.*, **3**, 297 (1870).

⁴⁸⁷ Pawlewski, *Ber.*, **31**, 661 (1898); *Ber.*, **35**, 110 (1902); Eibner, *Ber.*, **34**, 657 (1901).

react with alcohols⁴⁸⁸ to give esters and are rapidly hydrolyzed in the presence of moisture; the hydrolysis occurs so readily that thio acids may be used⁴⁸⁹ in place of hydrogen sulfide in analysis.

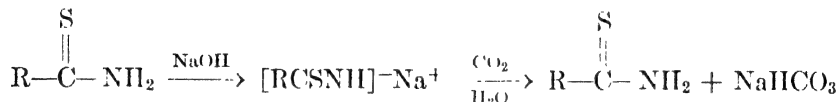


Thioacetic acid reacts readily with olefins^{68, 72b, 465} giving thiol esters resulting from "abnormal addition" (p. 639).

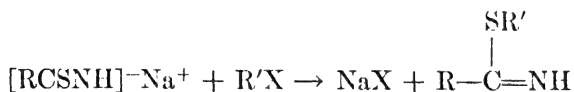


The thio acids are oxidized by atmospheric oxygen and are converted to diacyl disulfides by mild oxidizing agents (p. 935).

Reactions of Thioamides. The thioamides, in contrast to their oxygen analogs, are weak acids; they dissolve in aqueous alkali and may be reprecipitated by passing carbon dioxide into the alkaline solution.^{480, 490}



The salts of the thioamides may be isolated; they react with alkylating agents⁴⁶⁸ to give S-alkylisothioamides (imino thio esters).



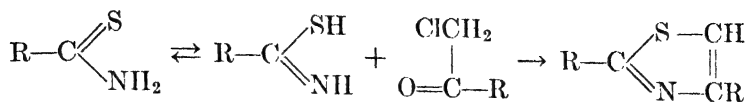
One of the most useful reactions of thioamides is that with α -halogen aldehydes or ketones to give thiazoles.⁴⁹¹ The results of this reaction, as well as the salt formation noted above, suggest that the thioamides are tautomeric.

⁴⁸⁸ Wheeler, *J. Am. Chem. Soc.*, **23**, 443 (1901); Stewart and McKinney, *ibid.*, **53**, 1482 (1931).

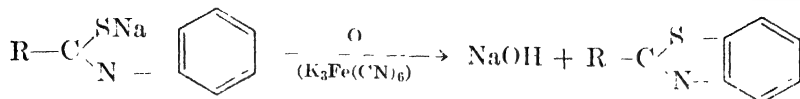
⁴⁸⁹ Schiff and Tarugi, *Ber.*, **27**, 3437 (1894); Yoe and Wirsing, *J. Am. Chem. Soc.*, **54**, 1866 (1932).

⁴⁹⁰ Nef, *Ann.*, **280**, 297 (1894).

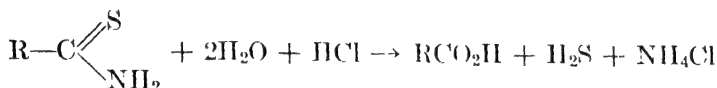
⁴⁹¹ Hantzsch, *Ann.*, **250**, 262 (1889).



Benzothiazoles have been obtained by the oxidation ⁴⁹² of thioanilides.



Thioamides are readily hydrolyzed ⁴⁹³ by heating with aqueous acid or alkali; they may also be converted to nitriles by elimination of hydrogen sulfide.⁴⁹⁴

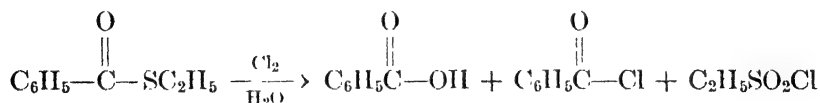


A characteristic blue color, probably due to thiobenzophenone, is formed ⁴⁹⁵ when thioamides are heated with benzophenonedichloride; this may be used as a test for thioamides.

Reactions of Other Compounds. Thio acid chlorides react in the same way as their oxygen analogs but are less stable.⁴⁶⁰ Thio anhydrides are readily hydrolyzed. Dithio acids are oxidized by air ⁴⁹⁶ or mild ox-

dizing agents ⁴⁹⁷ to thioacyl disulfides $\left(\text{R}-\overset{\text{S}}{\underset{\parallel}{\text{C}}}-\text{S}-\overset{\text{S}}{\underset{\parallel}{\text{C}}}-\text{R} \right)$; these may be used ⁴⁹⁸ for the acylation of amines.

The only characteristics of thion esters which are worthy of note are their rearrangement,⁴⁵¹ the ease with which the sulfur atom is removed, and their hydrolysis.⁴⁷¹ Thiol esters may also be hydrolyzed (pp. 843, 848) and are oxidized ²⁶⁷ by aqueous halogens.



Dithio esters undergo ammonolysis with concentrated ammonium hydroxide.⁴²²

⁴⁹² Jacobsen, *Ber.*, **19**, 1067 (1886); *Ber.*, **20**, 1895 (1887), Jacobsen and Ney, *Ber.*, **22**, 904 (1889).

⁴⁹³ Blank, *Ber.*, **25**, 3040 (1892).

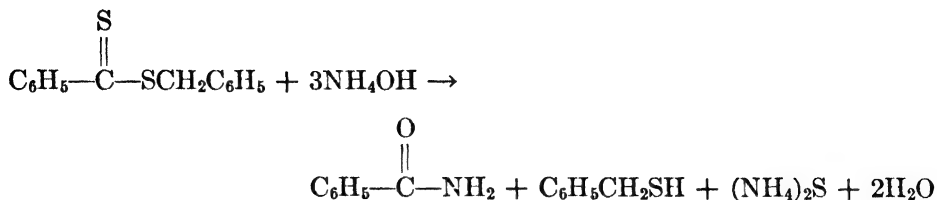
⁴⁹⁴ Jorgensen, *J. prakt. Chem.*, [2] **66**, 33 (1902).

⁴⁹⁵ Tschugaeff, *Ber.*, **35**, 2482 (1902).

⁴⁹⁶ Houben and Pohl, *Ber.*, **40**, 1303 (1907).

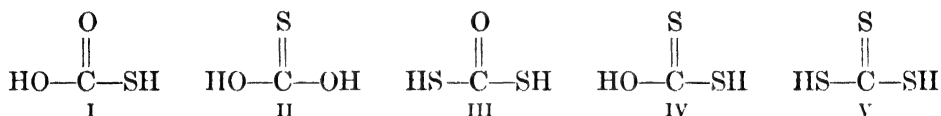
⁴⁹⁷ Bloch, Hohn, and Bugge, *J. prakt. Chem.*, **82**, 473 (1910).

⁴⁹⁸ Szperl and Wasilewska, *Roczniki Chem.*, **16**, 204 (1936) [*C. A.*, **30**, 8189 (1936)].

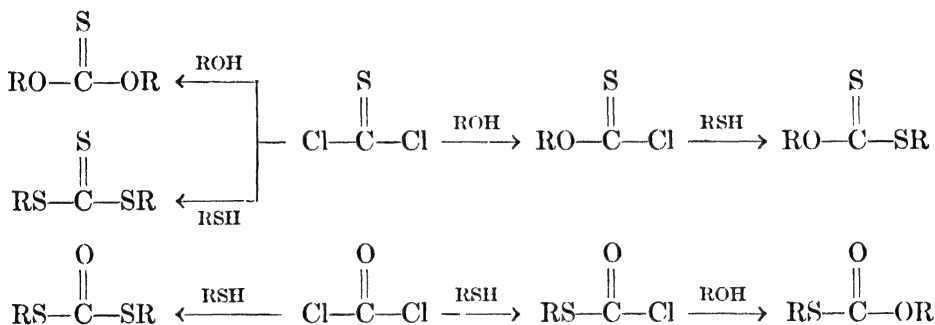


Derivatives of Carbonic Acid

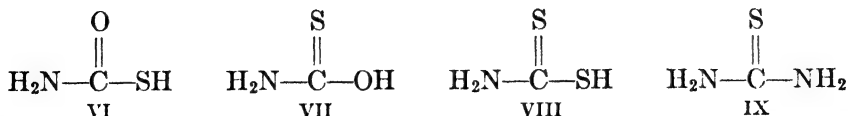
The sulfur analogs of carbonic acid offer structural possibilities which are not found in any of the other acids. In addition to the usual thiol (I) and thion (II), there are theoretically two dithio acids: a dithiol (III) and a thionthiol (IV) acid. There may also, in this case, be derivatives of a trithio acid (V).



Though these acids are unstable, their salts and other derivatives are known. For example, the esters of all of these may be prepared by the reaction of phosgene or thiophosgene with the proper alcohol or mercaptan.

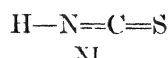
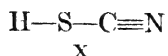


The thio derivatives of carbamic acid are the same in number as those from ordinary acids: thiocarbamates (VI), thioncarbamates (VII), and dithiocarbamates (VIII). Thiourca (IX) is the only thio-diamide of the series.



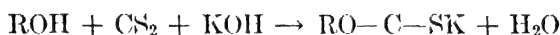
Elimination of the elements of water or ammonia from these amides

leads to two types of structure which cannot be derived from other thio acids: thiocyanic acid (X) and isothiocyanic acid (XI).



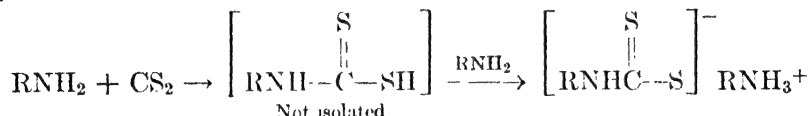
In general, the thio derivatives of carbonic acid behave as might be expected from the information already given about thio acid derivatives and from knowledge of the simple carbonates. Therefore, no attempt will be made to discuss the entire series; the following treatment will be limited to a few specific types or individual compounds which seem especially important or interesting.

Xanthates. The salts of O-alkyl derivatives of IV are known as xanthates.* They are obtained⁴⁹⁹ by the reaction of an alcohol with carbon disulfide † in the presence of alkali.



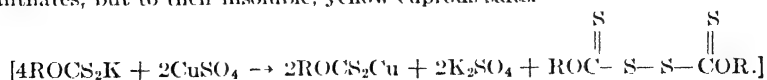
The xanthates from *n*-butyl and isoamyl alcohols have been used in flotation. The xanthates may be alkylated by the usual reagents; the esters of low molecular weight obtained by this method show the property of chemiluminescence in air.⁵⁰⁰ The most important application of the xanthates is the viscose process (p. 1683) for rayon and cellophane.

Dithiocarbamates. Carbon disulfide reacts with ammonia and with primary and secondary aliphatic amines to give salts of dithiocarbamic acid.



Alkali metal salts may be obtained by the use of alkali in the reaction of the amine with carbon disulfide. The dithiocarbamates are readily oxidized to thiuram disulfides, and these may be converted to sulfides. The thiuram disulfide and sulfide obtained from dimethylamine are known as "Tuads" and "Thionex" respectively and are important accel-

* The name is derived from the Greek (*xanthos*, yellow). It does not refer to the color of all xanthates, but to their insoluble, yellow cuprous salts.

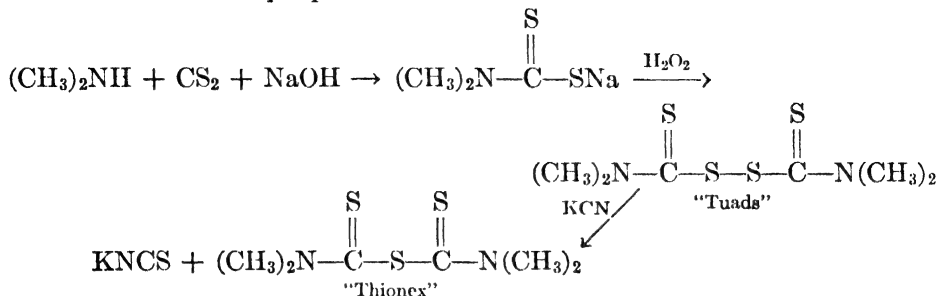


⁴⁹⁹ Zeise, *Ann.*, **16**, 178 (1835).

† Carbon oxysulfide undergoes a similar reaction, yielding a product known as "Bender's salt"; $\text{C}_2\text{H}_5\text{OH} + \text{COS} + \text{KOH} \rightarrow \text{H}_2\text{O} + \text{C}_2\text{H}_5\text{OCOSK}$. [Weeldenburg, *Rec trav chim.*, **47**, 496 (1928)]

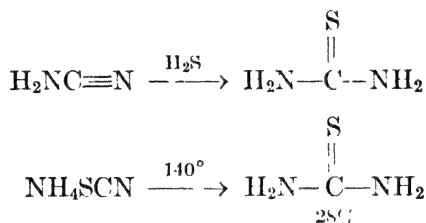
⁵⁰⁰ Delepine, *Bull. soc. chim.*, [4] **7**, 404 (1910).

erators for rubber vulcanization. The thiuram disulfide from piperidine is also used for this purpose.

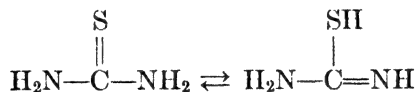


The reaction of aromatic primary and secondary amines with carbon disulfide gives derivatives of thiourea.

Thiourea. Thiourea (thiocarbamide) may be prepared by reactions analogous to those used for the synthesis of urea: the addition of hydrogen sulfide to cyanamide⁵⁰¹ or the use of ammonium thiocyanate in the Wöhler synthesis. In the second method, higher temperatures are required and the equilibrium is less favorable⁵⁰² than in the rearrangement of ammonium cyanate.



The reaction of thiourea with alkylating agents (p. 841), producing S-alkylisothiureas ("pseudothiureas"), suggests that thiourea may be tautomeric (compare with the other thioamides, p. 936).



The absorption spectrum of thiourea⁵⁰³ resembles that of $\text{R}_2\text{N}-\text{C}(=\text{NR})$

more than that of $\text{R}_2\text{N}-\text{C}(=\text{S})-\text{NR}_2$. However, the pH of solutions of

⁵⁰¹ Buchanan and Barsky, *J. Am. Chem. Soc.*, **52**, 195 (1930); Barsky and Buchanan *ibid.*, **53**, 1270 (1931); Barsky, *Chimie & Industrie*, **23**, 1032 (1932).

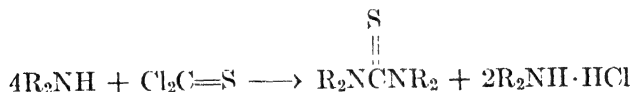
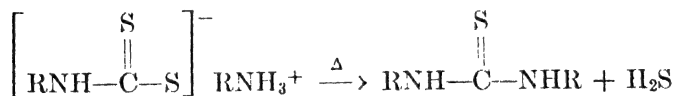
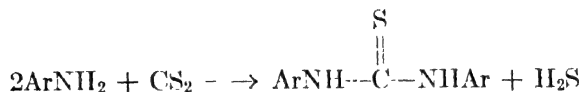
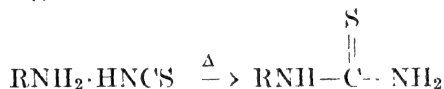
⁵⁰² Kappanna, *Quart. J. Indian Chem. Soc.*, **4**, 217 (1927) [*C. A.*, **21**, 3526 (1927)].

⁵⁰³ Rivier and Borel, *Helv. Chim. Acta*, **11**, 1219 (1928).

S

thiourea⁵⁰⁴ and its acyl derivatives⁵⁰⁵ indicate that the thion $\text{—}\ddot{\text{C}}\text{—}$ structure is predominant. Spectroscopic and x-ray data⁵⁰⁶ indicate that in the solid form, at least, thiourea and urea have similar structures.

Thiourea is useful in synthesis (p. 841) but has no large-scale commercial applications. With formaldehyde it gives products similar to urea-formaldehyde resins. Thiourea forms complex addition products⁵⁰⁷ with salts of the heavy metals and forms salts with strong mineral acids. Thiouronium nitrate is explosive. Thiourea is more readily acetylated than urea.⁵⁰⁸ It may be oxidized in acid solution to a strongly basic disulfide ($\text{H}_2\text{NC}(\text{:NH})\text{S—SC}(\text{:NH})\text{NH}_2$) and by further oxidation to a sulfonic acid,⁵⁰⁹ $\text{H}_2\text{NC}(\text{:NH})\text{SO}_3\text{H}$. Some of the thiobarbituric acids, obtained by condensing thiourea with substituted malonic esters, are powerful hypnotics.⁵¹⁰ Substituted thioureas may be prepared by heating amine thiocyanates, by the reaction of alkyl isothiocyanates with amines, by the reaction of aromatic amines with carbon disulfide, by heating the amine salts of dithiocarbamic acid, and by the reactions of amines with thiophosgene.



⁵⁰⁴ Cristol, Seigneurin, and Foucade, *Compt. rend.*, **200**, 2223 (1935).

⁵⁰⁵ Lecher and Siefken, *Ann.*, **456**, 192 (1927).

⁵⁰⁶ Demeny and Nitta, *Bull. Chem. Soc. Japan*, **3**, 128 (1928) [*C. A.*, **22**, 3073 (1928)], Wyckoff and Carey, *Z. Krist.*, **81**, 386 (1932) [*C. A.*, **26**, 4992 (1932)].

⁵⁰⁷ Dubsky, Okac, and Trtalek, *Mikrochemie*, **17**, 332 (1935).

⁵⁰⁸ Werner, *J. Chem. Soc.*, **109**, 1120 (1916).

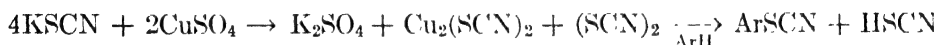
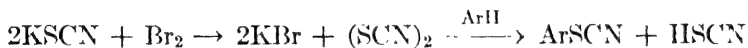
⁵⁰⁹ Boeseken, *Rec. trav. chim.*, **55**, 1040 (1936).

⁵¹⁰ Miller, Munch, Crossley, and Hartung, *J. Am. Chem. Soc.*, **58**, 1090 (1936); Tabern and Volwiler, *ibid.*, **57**, 1961 (1935).

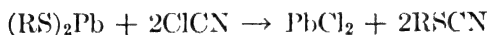
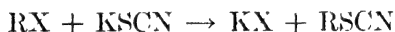
Diphenylthiocarbanilide (*sym.*-diphenylthiourea), prepared by the reaction of aniline with carbon disulfide, is an important rubber accelerator.

Thiocyanates. The reaction of potassium thiocyanate with potassium bisulfate results in the evolution of vapors which may be condensed to a white solid. Although this is called thiocyanic acid, it may be an equilibrium mixture of thiocyanic and isothiocyanic acids ($\text{H}-\text{S}-\text{C}\equiv\text{N} \rightleftharpoons \text{S}=\text{C}=\text{NH}$). It melts at about 5° and decomposes within a few minutes at room temperature. Concentrated solutions in dry organic solvents can be kept only at low temperatures, but dilute solutions are more stable.⁵¹¹

Thiocyanogen ($\text{N}\equiv\text{C}-\text{S}-\text{S}-\text{C}\equiv\text{N}$) may be obtained by the reaction of metallic thiocyanates with halogens. In its use for the estimation of unsaturation⁵¹² and in its reactions with aromatic compounds⁵¹³ it is analogous to the halogens; thiocyanogen has been called a pseudo-halogen.⁵¹⁴ Good yields of aryl thiocyanates are obtained by treating a metallic thiocyanate and an aromatic compound with bromine⁵¹⁵ or copper sulfate.⁵¹⁶



Alkyl thiocyanates, RSCN , are relatively stable but upon heating may isomerize to isothiocyanates. They are usually prepared by alkylation of a salt of thiocyanic acid;⁵¹⁷ a few have been obtained by the reaction of mercaptides with cyanogen chloride.



Alkyl thiocyanates may be oxidized to sulfonic acids (p. 889) and reduced to mercaptans.⁵¹⁸ Lauryl thiocyanate,⁵¹⁹ $\text{C}_{12}\text{H}_{25}\text{SCN}$, and butyl carbitol thiocyanate, $\text{C}_4\text{H}_9\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{SCN}$ ("Lethane"), are important insecticides which have been recently developed.

⁵¹¹ Kaufmann and Kögler, *Ber.*, **58**, 1553 (1925).

⁵¹² Caldwell and Piontkowski, *J. Am. Chem. Soc.*, **56**, 2086 (1934).

⁵¹³ Dienske, *Rec. trav. chim.*, **46**, 154 (1927).

⁵¹⁴ Kaufmann and Liepe, *Ber.*, **57**, 923 (1924).

⁵¹⁵ Kaufmann and Oehring, *Ber.*, **59**, 187 (1926).

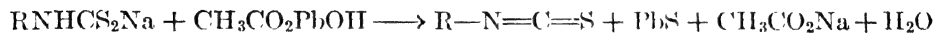
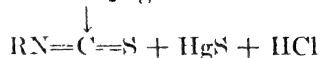
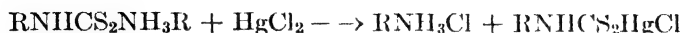
⁵¹⁶ Kaufmann and Kuchler, *Ber.*, **67**, 944 (1934).

⁵¹⁷ Delepine and Joffeux, *Compt. rend.*, **172**, 158 (1921).

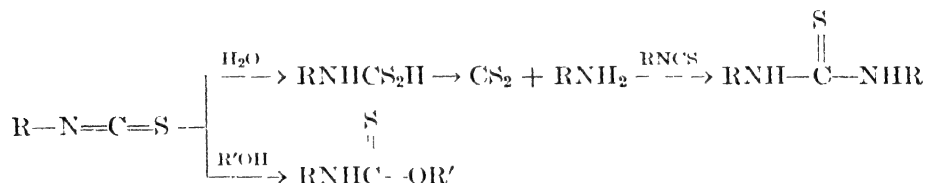
⁵¹⁸ Hofmann, *Ber.*, **1**, 169 (1868).

⁵¹⁹ Bousquet, Salzberg, and Dietz, *Ind. Eng. Chem.*, **27**, 1342 (1935).

Isothiocyanates. Alkyl isothiocyanates, also called "mustard oils," have a characteristic sharp odor and biting taste. They are usually obtained by the rearrangement of thiocyanates or by heating dithiocarbamates with mercuric chloride⁵¹⁸ or basic lead acetate.⁵²⁰



The reactions of isothiocyanates are analogous to those of isocyanates. Isothiocyanates react with water to give disubstituted thioureas, with alcohols to give thioncarbamates, with amines to give thioureas, and with the Grignard reagent (p. 934) to give thioamides.



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Acknowledgment. The author is greatly indebted to Dr. E. Emmet Reid for his generous assistance, and to Dr. Eugene Barr, Rohm and Haas Research Assistant at the University of Pennsylvania, for many helpful comments and for his aid in checking the literature references.

⁵²⁰ Delepine, *Bull. soc. chim.*, [4] **3**, 641 (1908).

CHAPTER 11
ALIPHATIC FLUORIDES

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INTRODUCTION

Organic fluorides have been prepared by a variety of methods, and their properties were investigated with varying thoroughness from 1843 until 1930. The most accurate work has long remained accessible in abstract form only, and this probably explains why the fluorides acquired the undeserved reputation of dangerous laboratory curiosities. After 1930, however, the commercialization of polyfluorides as refrigeration agents in household devices and, more strikingly, their use in air-conditioning equipment brought a sudden, perhaps overenthusiastic, interest in these compounds and a tendency to regard all fluorides as harmless, inert compounds. From about 1938 to date more critical studies have made it possible to classify the degree of chemical activity of the various fluorides, to take advantage of their activity as well as their inertness, and to present a coherent picture of the subject as a whole.

One finds that, after the classical pioneering of Moissan was completed around 1900, worthwhile contributions in the next twenty-five years were practically limited to the investigations of Frédéric Swarts. Since 1925 more numerous and more critical publications have appeared. The present survey aims at a comprehensive picture of the field as of January 1, 1941. In order to avoid duplication, it leaves the description of details, academic curiosities, and studies that are interesting but not general in nature to preceding compilations.*

The presentation is almost completely limited to aliphatic compounds, because aromatic fluorides have chemical, physiological, and physical properties which are more or less predictable from the known trends of the other aromatic halides, whereas aliphatic compounds may or may not show the characteristics to be expected by analogy. The aliphatic compounds have also been used in more original applications.

METHODS OF PREPARATION

All the methods known to introduce halogen atoms into organic molecules can be used to synthesize fluorides. All of them, however, have important limitations. At the present moment the method most generally used is the interchange of halogen atoms between an organic halide and an inorganic fluoride; second in practical importance is the addition of hydrogen fluoride to a double or triple bond, a method which is yet in its infancy, but is growing fast.

* Key references may be found at the end of the chapter.

Direct Fluorination. Most organic substances burn or explode when introduced into a fluorine atmosphere. Carbon gives mostly carbon tetrafluoride, but also small quantities of other compounds (C_2F_6 , C_2F_4 , C_3F_8) and apparently higher homologs C_nF_{2n+2} .^{1, 2, 3, 4} Some cyclic compounds have been claimed but in an unconvincing fashion. Hydrocarbons can be fluorinated in the gaseous form over copper gauze by means of fluorine diluted by nitrogen; and a variety of reaction products obtained by the replacement of hydrogen by fluorine in the original hydrocarbon, and its decomposition products, have been listed.^{5, 6, 7, 8, 9} The hydrogen atoms, the chlorine atom, or both elements may be replaced in ethyl chloride.¹⁰ Organic polyhalides undergo partial replacement of the halogens, and ethylenic or aromatic polyhalides give products of addition as well as substitution.^{11, 12, 13}

Liquid or dissolved paraffins and halogenated derivatives have repeatedly been subjected to fluorine, but without much success and with many accidents due to accumulation of unreacted fluorine: successful results have, however, been obtained by causing the fluorine action to take place at the surface of the liquid^{14, 15, 16} or in an inert solvent.¹⁷ General indications have been obtained that the fluorination of fatty acids occurs mostly in the β - and γ -positions, and it has been claimed that the hydrogen atoms in an α -position are protected by the adjacent carboxyl group.^{14, 15} Olefins and olefinic acids have given very small yields of difluorides.^{14, 15} Other compounds have given indefinite, fluorine-containing products.

This method seems to have some limitations.

(a) When it is used to replace hydrogen, it inevitably consumes one-half of the fluorine, the most valuable reagent, to manufacture hydrogen fluoride, a cheaper by-product. The reaction products are frequently difficult to separate from the starting material as well as from each other.

¹ Moissan, *Compt. rend.*, **110**, 276 (1890).

² Lebeau and Damiens, *ibid.*, **182**, 1340 (1926).

³ Ruff and Kern, *Z. anorg. allgem. Chem.*, **192**, 249 (1930).

⁴ Simons and Block, *J. Am. Chem. Soc.*, **59**, 1407 (1937); **61**, 2964 (1939).

⁵ Bigelow, Pearson, Cook, and Miller, *ibid.*, **55**, 4614 (1933).

⁶ Calfee and Bigelow, *ibid.*, **59**, 2072 (1937).

⁷ Calfee, Fukuhara, and Bigelow, *ibid.*, **61**, 3552 (1939).

⁸ Young, Fukuhara, and Bigelow, *ibid.*, **62**, 1171 (1940).

⁹ Hadley and Bigelow, *ibid.*, **62**, 3302 (1940).

¹⁰ Calfee, Fukuhara, Young, and Bigelow, *ibid.*, **62**, 267 (1940).

¹¹ Bigelow and Pearson, *ibid.*, **56**, 2773 (1934).

¹² Miller, Calfee, and Bigelow, *ibid.*, **59**, 198 (1937).

¹³ Fukuhara and Bigelow, *ibid.*, **60**, 427 (1938).

¹⁴ Fredenhagen and Cadenbach, *Ber.*, **67**, 928 (1934).

¹⁵ Bockemüller, *Ann.*, **506**, 20 (1933).

¹⁶ Miller, *J. Am. Chem. Soc.*, **62**, 341 (1940).

¹⁷ Calcott and Benning, U. S. pat. 2,013,030 [*C.A.*, **29**, 6900 (1935)].

The heat of reaction is greater than the energy required to break a carbon-to-carbon linkage.

(b) To replace halogen atoms, the action of free fluorine does not have any advantage over other methods which are cheaper, more convenient, and less dangerous.

(c) In all cases the number of substitutions and the location of the fluorine atoms in the reaction products have been unpredictable and their precise control is not yet available. The purity of the fluorine is of great importance, and stress has been placed on the adverse effect of small amounts of oxides.

Esterification of an Alcohol. It is possible but entirely impracticable to esterify an alcohol with concentrated aqueous hydrofluoric acid, because the saponification of the monofluorides is far too preponderant. It is equally impracticable to circumvent this by removal of water, because all the desiccating agents tried have caused the decomposition of the fluorides into olefins and hydrogen fluoride. The same objection, as well as the formation of ethers, defeats attempts to interact alcohols with an excess of anhydrous hydrogen fluoride. Finally, a roundabout procedure such as the use of a phosphorus fluoride leads only to esters of phosphoric acid. These obstacles explain why the synthesis of fluorides by esterification has been almost completely abandoned.

Addition of Hydrogen Fluoride. The addition of hydrogen fluoride is a new procedure which offers much promise. Acetylene itself reacts with difficulty, at room temperature, to give a mixture of vinyl fluoride and asymmetrical difluoroethane, but the higher alkynes react readily at -70° to -60° to give 2,2-difluoroalkanes exclusively.¹⁸ The main problem is to obtain the completion of the addition reaction and at the same time prevent the formation of resinous products.

Olefins and hydrogen fluoride have been successfully combined.^{19, 20} The addition invariably yields a secondary or a tertiary fluoride, but never a primary compound except, of course, for the addition to ethylene itself. The practical problem is to hinder the reversal of the reaction, which is particularly likely to occur with tertiary fluorides and is enhanced by heat or the presence of acids. This difficulty disappears when the olefin already carries a halogen atom on one of the doubly linked carbon atoms: for instance, vinyl chloride yields stable CH_3CHClF , while $\text{CH}_3\text{CH}=\text{CCl}_2$ very easily gives $\text{CH}_3\text{CH}_2\text{CCl}_2\text{F}$, and $\text{CH}_3\text{CCl}=\text{CHCl}$ yields $\text{CH}_3\text{CClFCH}_2\text{Cl}$ quantitatively.²¹ In all cases, the rule of Mar-

¹⁸ v. Grosse and Lind, Baltimore meeting of the American Chemical Society, 1939.

¹⁹ v. Grosse and Lind, *J. Org. Chem.*, **3**, 26 (1938).

²⁰ v. Grosse, Wacker, and Lind, *J. Phys. Chem.*, **44**, 275 (1940).

²¹ Henne and Whaley, unpublished results.

kownikoff and the theory of Kharasch²² are verified, and so far it has been impossible to reverse the direction of addition. The patent literature^{23, 24} describes the addition of hydrogen fluoride to oleic and stearolic acids, to yield fluoro and difluorostearic acids, respectively. These are reported as stable compounds, a claim which it would be interesting to confirm.

Cyclopropane combines with hydrogen fluoride to give normal propyl fluoride.¹⁹ Good control of the experimental conditions is essential because, when cyclopropane and hydrogen fluoride interact too suddenly, the resulting normal propyl fluoride decomposes into hydrogen fluoride and propylene, and when these two compounds recombine they yield isopropyl fluoride. Therefore, a lack of precautions may lead to a mixture of reaction products and to an incorrect interpretation.

Substitution Methods. The principle of the substitution methods consists in causing a double exchange to take place between an organic halide and an inorganic fluoride, or between an organic sulfate and an inorganic fluoride. Sulfates are very rarely used, and the original synthesis of methyl fluoride from dimethyl sulfate and potassium fluoride is now of historical importance only. When the organic halogen to be substituted is chemically very active, the substitution is usually quite simple; for instance, an acyl halide is transformed into the corresponding acyl fluoride by means of antimony fluoride, hydrogen fluoride,²⁵ or even potassium fluoride in hot acetic anhydride.²⁶ Similarly, sulfonyl fluorides are conveniently obtained from sulfonyl chlorides and zinc fluoride.²⁷

Alkyl monohalides are converted to the fluorides by agents such as silver, mercurous, or mercuric fluorides. In most laboratories it is more convenient to use a fluoride of mercury.^{28, 29, 30, 31} Organic polyhalides with several halogen atoms located on the same carbon atom are best treated with antimony trifluoride, pentavalent antimony fluorochlorides, or similar inorganic fluorides. Antimony trifluoride seldom acts efficiently by itself, but a small quantity of pentavalent salt, acting as "fluorine carrier," permits the exchange of halogen atoms to proceed to completion. Antimony fluorochloride is used for very difficult substitu-

²² Kharasch, Engelman, and Mayo, *J. Org. Chem.*, **2**, 298 (1937).

²³ I. G. Farben Industrie, Fr. pat. 799,432 [*C.A.*, **30**, 7585 (1936)].

²⁴ I. G. Farben Industrie, Fr. pat. 786,112. Ger. pat. 621,977 [*C.A.*, **30**, 2314 (1936)].

²⁵ Fredenhagen and Cadenbach, *Z. physik. Chem.*, **A164**, 201 (1933).

²⁶ Nesmeyanov and Kahn, *Ber.*, **67**, 370 (1934).

²⁷ Davies and Dick, *J. Chem. Soc.*, **483**, 2042 (1932).

²⁸ Swarts, *Bull. classe sci. Acad. roy. Belg.*, [5] **22**, 781 (1936); *Bull. soc. chim. Belg.* **46**, 10 (1937).

²⁹ Henne and Renoll, *J. Am. Chem. Soc.*, **60**, 1060 (1938).

³⁰ Henne, *ibid.*, **60**, 1569 (1938).

³¹ Henne and Midgley, *ibid.*, **58**, 884 (1936).

tions. Hydrogen fluoride can act as the source of fluorine for organic di- or tri-halides whose halogen atoms are all linked to a single carbon atom: examples are the conversion of $\text{C}_6\text{H}_5\text{CCl}_3$ to $\text{C}_6\text{H}_5\text{CF}_3$, CH_3CCl_3 to CH_3CF_3 , and $\text{CH}_3\text{CCl}_2\text{CH}_3$ to $\text{CH}_3\text{CF}_2\text{CH}_3$.

Limitations of Substitution Methods. Antimony fluoride, which is by far the most widely used agent, acts as follows: in the methane series it converts CCl_4 to CCl_3F and CCl_2F_2 very readily. Extremely small amounts of CClF_3 have been obtained at high temperature and high pressure in the laboratory, and also as a minor by-product in the industrial manufacturing of CCl_2F_2 . Similarly, chloroform is easily transformed into CHCl_2F and CHClF_2 , but not into fluoroform,³² and attempts to use large proportions of antimony fluorochlorides at high temperature cause decomposition and substitution of the hydrogen by chlorine. Methylene chloride is easily transformed into CH_2F_2 , though much decomposition occurs.³² Methyl chloride is not affected by antimony fluoride. It is thus clear that, in the methane series, two fluorine atoms and no more are easily introduced by antimony fluoride into polyhalides. If this limitation is to be circumvented, it is necessary to call a different fluorinating agent into play when the limits of antimony fluoride have been reached: for example, fluoroform is efficiently made from CHBrF_2 ,³³ and methyl fluoride from methyl chloride by means of mercuric fluoride.

In the ethane series, the action of antimony fluoride has limitations of position, in addition to the limitations of extent. Hexachloroethane gives the following fluorides: $\text{CCl}_3\text{CCl}_2\text{F}$; $\text{CCl}_2\text{FCCl}_2\text{F}$; $\text{CCl}_2\text{FCClF}_2$; and $\text{CClF}_2\text{CClF}_2$; an entirely symmetrical course is thus evident.³⁴ The presence of hydrogen in the molecule markedly alters the course as well as the extent of the halogen exchange. Pentachloroethane gives $\text{CHCl}_2\text{CCl}_2\text{F}$ then $\text{CHCl}_2\text{CClF}_2$ easily, but the next substitution is very difficult to perform and the formula of the resulting trifluoride has not been convincingly established.³⁵ Acetylene tetrachloride yields $\text{CHCl}_2\text{CHClF}$, then $\text{CHCl}_2\text{CHF}_2$ relatively easily. The third step was originally reported by Swarts³⁶ to be CHClFCHF_2 , a compound boiling at 17° ; although this was certainly correct, under the experimental conditions used,* all efforts at duplication in a laboratory as well as on an industrial scale have always yielded CH_2ClCF_3 , a compound boiling at 6° .³⁷ An explanation of this anomaly is offered which consists of a parting

³² Henne, *ibid.*, **59**, 1400 (1937).

³³ Henne, *ibid.*, **59**, 1200 (1937).

³⁴ Locke, Brode, and Henne, *ibid.*, **56**, 1726 (1934).

³⁵ Henne and Ladd, *ibid.*, **58**, 402 (1936).

³⁶ Swarts, *Mém. Acad. roy. Belg.*, **61**, 1-94 (1901).

* Dr. Swarts attributed many of his excellent results to the use of platinum equipment (Private communication.)

³⁷ Henne and Renoll, *J. Am. Chem. Soc.*, **58**, 887 (1936).

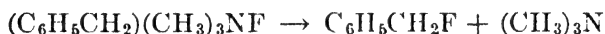
of $\text{CHCl}_2\text{CHF}_2$ into HCl and $\text{CHCl}=\text{CF}_2$, followed by an addition of HF or HCl to give $\text{CH}_2\text{ClCClF}_2$ and CH_2ClCF_3 . It is to be noted that the rearrangement can be avoided by using, as the source of fluorine, mercuric fluoride, which gives the sequence normally expected, $\text{CHBr}_2\text{CHF}_2 \rightarrow \text{CHBrFCHF}_2 \rightarrow \text{CHF}_2\text{CHF}_2$.³⁷

Other ethane derivatives give the following results: ^{37, 38, 39} $\text{CH}_2\text{ClCHCl}_2 \rightarrow \text{CH}_2\text{ClCHClF}$ and $\text{CH}_2\text{ClCHF}_2$; $\text{CH}_3\text{CCl}_3 \rightarrow \text{CH}_3\text{CCl}_2\text{F}$, CH_3CClF_2 , and CH_3CF_3 ; $\text{CH}_3\text{CHCl}_2 \rightarrow \text{CH}_3\text{CHClF}$ and CH_3CHF_2 ; $\text{CH}_3\text{CH}_2\text{Cl} \rightarrow$ no reaction. Mercury and silver fluorides can overcome the limitations, as in the methane derivatives.

To sum up, the following main trends of the ethane series can be listed: (1) the ease of transforming a CCl_3 group into a CClF_2 group; (2) the rarity of forming CF_3 groups; (3) the resistance of CHCl_2 groups, particularly when they are adjacent to a group already fluorinated.

An examination of the propane series^{21, 40, 41, 42, 43, 44} confirms and enlarges these findings. Octachloropropane gives successively $\text{CCl}_2\text{FCCl}_2\text{CCl}_3$, $\text{CCl}_2\text{FCCl}_2\text{CCl}_2\text{F}$, $\text{CClF}_2\text{CCl}_2\text{CCl}_2\text{F}$, and $\text{CClF}_2\text{CCl}_2\text{CClF}_2$. This confirms the reactivity of the CCl_3 group and parallels closely the behavior of C_2Cl_6 . Asymmetrical heptachloropropane gives $\text{CHCl}_2\text{CCl}_2\text{CCl}_2\text{F}$, $\text{CHCl}_2\text{CCl}_2\text{CClF}_2$, $\text{CHCl}_2\text{CClFCClF}_2$, and CHClFCClFCClF_2 . This indicates the sluggishness of the $-\text{CCl}_2-$ group, the difficulty of replacing both halogen atoms by fluorine, and it confirms the resistance of CHCl_2 to fluorine exchange as already observed in the ethane series. Dichloropropane, $\text{CH}_3\text{CCl}_2\text{CH}_3$, gives $\text{CH}_3\text{CF}_2\text{CH}_3$, and trichloropropane, $\text{CH}_3\text{CH}_2\text{CCl}_3$, gives $\text{CH}_3\text{CH}_2\text{CF}_3$ with great ease; these cases are similar to that of CH_3CCl_3 which is very easily converted to CH_3CF_3 ; in each instance, all the halogens are placed on a single carbon atom.

Decomposition of a Quaternary Ammonium Fluoride. This method is very limited in its application, but it allowed Ingold⁴⁵ to prepare benzyl fluoride with a 60 per cent yield as follows:



Introduction of Fluorine into a Benzene Ring. Aromatic fluorides are best prepared by way of a diazonium compound. An amine can be diazotized in hydrofluoric acid solution, and the diazonium fluoride decomposed to the corresponding aryl fluoride, with simultaneous

³⁸ Henne and Renoll, *ibid.*, **58**, 889 (1936).

³⁹ Henne and Hubbard, *ibid.*, **58**, 404 (1936).

⁴⁰ Henne and Renoll, *ibid.*, **59**, 2434 (1937).

⁴¹ Henne and Ladd, *ibid.*, **60**, 2491 (1938).

⁴² Henne, Renoll, and Leicester, *ibid.*, **61**, 938 (1939).

⁴³ Henne and Renoll, *ibid.*, **61**, 2489 (1939).

⁴⁴ Henne and Haackl, *ibid.*, **63**, 3476 (1941).

⁴⁵ Ingold and Ingold, *J. Chem. Soc.*, 2249 (1928).

evolution of nitrogen. The literature, however, is full of contradictory indications as to yields and by-products. Nevertheless, good yields can be obtained by using an exceedingly large excess of concentrated acid, or by carrying out the diazotization with solid sodium nitrite in anhydrous hydrogen fluoride. This last procedure offers attractive industrial advantages.

Neither method is practicable in most laboratories, and it is more convenient to resort to one of the following modifications. The older one ⁴⁶ consists in forming a coupled product of the diazonium compound with a secondary aliphatic amine, usually piperidine. The resulting diazopiperidide, $\text{ArN}:\text{N}(\text{C}_4\text{H}_9)_2$, is easily decomposed about room temperature by concentrated hydrofluoric acid into piperidine hydrofluoride and an aryl fluoride. The latter is obtained in yields of around 50 per cent, and the former can be recovered for subsequent operations. The yields are very sensitive to impurities. The newer methods ^{47, 48} consist in isolating some insoluble diazonium double fluoride, the most convenient of which is a borofluoride. The solution of diazonium salt is treated with sodium borofluoride, to form an insoluble crystalline borofluoride, ArN_2BF_4 , which is stable, easily separated, recrystallized, and dried. On gentle heating it decomposes at a definite temperature into an aryl fluoride, nitrogen, and boron fluoride, which can be recovered. The yields, which are frequently excellent, are influenced by the groups present on the benzene ring.

EFFECT ON PHYSICAL PROPERTIES

In general, fluorine affects physical properties such as density, refractive index, or viscosity in the same manner as the other halogens do, but the effect is much smaller than that of chlorine. By contrast, fluorine has an exceedingly strong influence on the boiling point and on the melting point; and the magnitude as well as the direction of its effect are entirely out of line with the other halogens.

Density. The replacement of hydrogen by fluorine increases the density by progressively decreasing increments.

Viscosity. The experimental data have been obtained and critically discussed by Swarts,⁴⁹ who found only approximate, empirical rules rather than definite additive properties. The viscosities of some industrially used fluorides have also been reported.^{50, 51}

⁴⁶ Wallach, *Ann.*, **235**, 255 (1886); Wallach and Hensler, *Ann.*, **243**, 219 (1888).

⁴⁷ Balz and Schiemann, *Ber.*, **60**, 1180 (1927).

⁴⁸ Meigs, U. S. pat. 1,916,327 [*C.A.*, **27**, 4539 (1933)].

⁴⁹ Swarts, *J. chim. phys.*, **28**, 622 (1931).

⁵⁰ Benning and Markwood, *Refrig. Eng.*, **37**, 243 (1939).

⁵¹ Hovorka and Geiger, *J. Am. Chem. Soc.*, **55**, 4760 (1933).

TABLE I
 DENSITY DIFFERENCES

| | <i>d</i> | Δd | | <i>d</i> | Δd |
|--|----------|------------|---|----------|------------|
| C ₆ H ₁₄ | 0.660 | 0.132 | C ₆ H ₅ C ₆ H ₅ | 1.156 | 0.091 |
| C ₄ H ₉ CHFCH ₃ | 0.792 | | <i>p</i> -C ₆ H ₅ C ₆ H ₄ F..... | 1.247 | |
| C ₄ H ₉ CF ₂ CH ₃ | 0.902 | | <i>p,p'</i> -C ₆ H ₄ FC ₆ H ₄ F.. | 1.336 | |
| C ₆ H ₆ | 0.871 | 0.151 | C ₆ H ₅ CH ₃ | 0.866 | 0.162 |
| C ₆ H ₅ F..... | 1.022 | | C ₆ H ₅ CH ₂ F..... | 1.028 | |
| <i>m</i> -C ₆ H ₄ F ₂ | 1.153 | 0.131 | C ₆ H ₅ CHF ₂ | 1.136 | 0.108 |
| | | | C ₆ H ₅ CF ₃ | 1.188 | |

Dielectric Constant and Dipole Moment. The first measurements of Watson^{52, 53} and Smyth⁵⁴ were critically examined, repeated, and enlarged by Fuoss,⁵⁵ who listed the following values for the dipole moments: CF₄, 0.0; CF₃Cl, 0.47; CF₂Cl₂, 0.55; CFCF₃, 0.53; CClF₂CClF₂, 0.0; CH₃CF₃, 2.27; CH₃CClF₂, 2.13; CF₃CF₂Cl, 0.14; and CF₃CH₂Cl, 1.64.

Refraction and Dispersion. These properties have been fully investigated by Swarts,⁵⁶ who compared a large number of fluorine derivatives with similar hydrogen compounds. His conclusion was that the refractive increment of fluorine is not very different from that of hydrogen, and that the value 1.0 seems most acceptable. He also found that the atomic dispersion of fluorine is exceedingly small, almost zero. Similar results are also reported by v. Grosse.²⁰

Parachor. Measurements made on aromatic substances⁵⁷ first gave an atomic value of 25.0 for the parachor increment of fluorine. Additional experimental data made it possible to compare the parachor of fluorinated substances with the corresponding hydrogenated substances⁵⁸ and to obtain a difference of 10.5 in aliphatic compounds, 9.3 in aromatic compounds, and 8.4 in CF₃ groups. If one accepts the constant value of

⁵² Watson, Rao, and Ramaswamy, *Proc. Roy. Soc. (London)*, **A143**, 558 (1934).

⁵³ Watson, Kane, and Ramaswamy, *ibid.*, **A156**, 137 (1936).

⁵⁴ Smyth and McAlpin, *J. Chem. Phys.*, **1**, 190 (1933).

⁵⁵ Fuoss, *J. Am. Chem. Soc.*, **60**, 1633 (1938).

⁵⁶ Swarts, *J. chim. phys.*, **20**, 30 (1923).

⁵⁷ Allen and Sugden, *J. Chem. Soc.*, 760 (1932).

⁵⁸ Desreux, *Bull. soc. chim. Belg.*, **44**, 249 (1935).

15.8 for hydrogen, it follows that the fluorine value is 26.3 in aliphatic compounds, 25.1 in aromatic compounds, and 24.2 in CF_3 groups.

Thermodynamic Properties. The thermodynamic properties of the fluorinated refrigerants have been well summarized by Buffington^{59, 60, 61, 62, 63} and by Benning,^{64, 65} who were interested in engineering applications for the refrigeration industry.

Boiling Point. Table II lists the boiling points of the chlorine and fluorine substitution products of methane.

TABLE II

| | | | | | | | | | |
|--------------------------|------|-------------------------|------|--------------------------|------|-----------------|------|---------------|-------|
| CCl_4 | 76° | CCl_3F | 25° | CCl_2F_2 | -29° | CClF_3 | -81° | CF_4 | -128° |
| CHCl_3 | 61° | CHCl_2F | 9° | CHClF_2 | -41° | CHF_3 | -83° | | |
| CH_2Cl_2 | 40° | CH_2ClF | -9° | CH_2F_2 | -52° | | | | |
| CH_3Cl | -24° | CH_3F | -78° | | | | | | |

In this methane series, the substitution of a chlorine atom by a fluorine atom lowers the boiling point by 51° on an average. A similar tabulation, using bromofluoro-derivatives, would indicate an average depression of 80°.

However, if one tabulates the compounds obtained by substituting fluorine for hydrogen in methane, one obtains a picture entirely different from that of the other halogens. Table III shows that the last two

TABLE III

| | B. P. | Difference | | B. P. | Difference |
|--------------------------------|-------|------------|-------------------------------|-------|------------|
| CH_4 | -161° | | CH_4 | -161° | |
| | | +137 | | | +83 |
| CH_3Cl | -24° | | CH_3F | -78° | |
| | | +64 | | | +26 |
| CH_2Cl_2 | +40° | | CH_2F_2 | -52° | |
| | | +21 | | | -31 |
| CHCl_3 | +61° | | CHF_3 | -83° | |
| | | +15 | | | -45 |
| CCl_4 | +76° | | CF_4 | -128° | |

⁵⁹ Buffington and Gilkey, *Ind. Eng. Chem.*, **23**, 364 (1931).

⁶⁰ Gilkey, Gerard, and Bixler, *ibid.*, **23**, 364 (1931).

⁶¹ Bichowsky and Gilkey, *ibid.*, **23**, 366 (1931).

⁶² Buffington and Fleischer, *ibid.*, **23**, 1290 (1931).

⁶³ Buffington and Gilkey, *ibid.*, **23**, 1292 (1931).

⁶⁴ Benning and McHarness, *ibid.*, **31**, 912 (1939); **32**, 497 (1940); **32**, 698 (1940); **32**, 814 (1940).

⁶⁵ Benning, McHarness, Markwood, and Smith, *ibid.*, **32**, 976 (1940).

fluorine substitutions actually lower the boiling point whereas other halogens invariably raise it. This raising and lowering of the boiling point caused by a substitution of fluorine for hydrogen is further illustrated by comparing the compounds of Table II in a diagonal fashion, as for instance:

| | | | | | | | | |
|------------|-----------------|-------------|------------------|------------|-------------------------|-------------|-----------------|-------------|
| B. P. | CClH_3 | -24° | CClFH_2 | -9° | CClF_2H | -41° | CClF_3 | -81° |
| Difference | | | +15 | | -32 | | -40 | |

The same general considerations prevail in the ethane series; that is, the substitution of a chlorine atom by a fluorine atom invariably causes a 42° depression, while the effect obtained by substituting fluorine for hydrogen atoms may be either a raising or a lowering of the boiling point, as shown in Fig. 1. In this case the second fluorine substitution

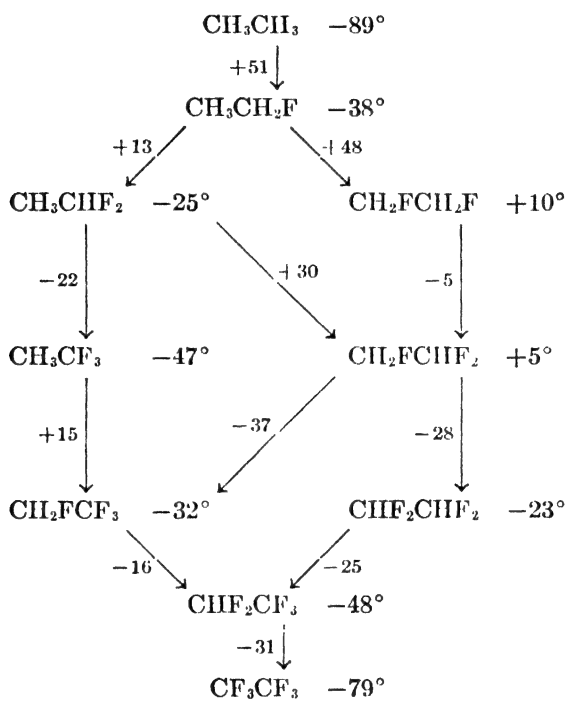


Fig. 1

still causes the boiling point to rise but by different quantities, depending on the place of the second fluorine in the molecule; the third and fourth substitutions raise or lower the boiling point, depending on the place of the substitution; the fifth and the sixth lower the boiling point. Higher members are subject to the same kind of observations, for which no satisfactory explanation has yet been advanced, and the same effect can be observed in the polar fluorides of Table IV.

TABLE IV

| | | | |
|------------------------------------|------|-----------------------------------|------|
| $\text{CH}_3\text{CH}_2\text{OH}$ | 78° | $\text{CH}_3\text{CO}_2\text{H}$ | 117° |
| $\text{CH}_2\text{FCH}_2\text{OH}$ | 103° | $\text{CH}_2\text{FCO}_2\text{H}$ | 165° |
| $\text{CHF}_2\text{CH}_2\text{OH}$ | 96° | $\text{CHF}_2\text{CO}_2\text{H}$ | 134° |
| $\text{CF}_3\text{CH}_2\text{OH}$ | 78° | $\text{CF}_3\text{CO}_2\text{H}$ | 72° |

The boiling points of homologs differ by about 30°, as shown in Table V.

TABLE V

| | | |
|---------------------------------------|-------|--|
| CH_2F_2 | - 52° | |
| CH_3CHF_2 | -25° | |
| $\text{C}_2\text{H}_5\text{CHF}_2$ | +6° | $\text{CH}_3\text{CF}_2\text{CH}_3$ 0° |
| | | $\text{CH}_3\text{CF}_2\text{C}_2\text{H}_5$ 31° |
| | | $\text{CH}_3\text{CF}_2\text{C}_3\text{H}_7$ 60° |
| $\text{C}_6\text{H}_{13}\text{CHF}_2$ | 120° | |

Freezing Point. Fully halogenated compounds invariably give well-defined, soft crystals. In contrast, compounds which contain hydrogen in their molecules thicken to a glass at low temperature and crystallize with difficulty if at all. However, compounds which accumulate all their hydrogen on some carbon atoms, and all the halogens on other carbon atoms, do crystallize easily, and their melting points are surprisingly high. For example, $\text{CH}_3\text{CF}_2\text{CCl}_3$ melts at +52°, while $\text{CCl}_3\text{CF}_2\text{CCl}_3$ melts at -5°. ^{43, 66, 67}

The homologous series of Table VI present alternating freezing points similar to those of the low paraffins.

TABLE VI

| | | | | | |
|-----------------------------------|-------|---------------------------|-------|---------------------------|-------|
| CF_3H | -163° | CF_4 | -186° | CH_4 | -183° |
| CF_3CH_3 | -107° | C_2F_6 | -100° | C_2H_6 | -172° |
| $\text{CF}_3\text{C}_2\text{H}_5$ | -148° | C_3F_8 | -183° | C_3H_8 | -187° |
| | | C_4F_{10} | -84° | C_4H_{10} | -135° |

Among fully halogenated compounds, the accumulation of the fluorine atoms at the ends of the molecule always causes the melting point to be higher than that of isomers with fluorine atoms spread over the several carbon atoms of the molecule, or accumulated in its middle. This effect is increased when the fluorine atoms become more numerous. Empirical rules based on analogies are easily derived, but satisfactory reasons have not yet been advanced.

⁶⁶ McBee, Henne, Hass, and Elmore, *J. Am. Chem. Soc.*, **62**, 3340 (1940).

⁶⁷ Henne, Wiest, and Haeckl, unpublished results.

TABLE VII
FREEZING POINTS

| Difluorides | | Trifluorides | | Tetrafluorides | |
|---|------|--|-------|--|------|
| $\text{CCl}_3\text{CCl}_2\text{CClF}_2$ | +50° | $\text{CCl}_3\text{CCl}_2\text{CF}_3$ | +109° | $\text{CCl}_2\text{FCCl}_2\text{CF}_3$ | +41° |
| $\text{CCl}_2\text{FCCl}_2\text{CCl}_2\text{F}$ | +30° | $\text{CCl}_2\text{FCCl}_2\text{CClF}_2$ | -5° | $\text{CClF}_2\text{CCl}_2\text{CClF}_2$ | -42° |
| $\text{CCl}_3\text{CF}_2\text{CCl}_3$ | -5° | $\text{CCl}_3\text{CClFCClF}_2$ | -18° | $\text{CCl}_2\text{FCClFCClF}_2$ | -58° |
| | | $\text{CCl}_2\text{FCF}_2\text{CCl}_3$ | -89° | $\text{CCl}_2\text{FCF}_2\text{CCl}_2\text{F}$ | -96° |

CHEMICAL PROPERTIES

Classification. In order satisfactorily to account for the chemical behavior of organic fluorides, it is convenient to divide them sharply into two classes, monofluorides and polyfluorides. Monofluorides are characterized by their instability and their tendency to lose hydrogen fluoride, which automatically generates an unsaturated residue and therefore gives rise to olefins, polymers, or condensation products. By contrast, polyfluorides are exceedingly stable and often physiologically inert; chemically, they are indifferent or sluggish and resist oxidation particularly well. These properties are so marked that they place the polyfluorides in a class by themselves. For instance, the physiological inertness of CCl_2F_2 has been illustrated by keeping animals for weeks in an artificial atmosphere of 20 per cent oxygen, 40 per cent nitrogen, and 40 per cent CCl_2F_2 without any visible effect. The resistance to oxidation can be illustrated by passing CF_3CH_3 through fuming nitric acid at 150° and recovering the trifluoride quantitatively.⁶⁸

It should be emphasized that a polyfluoride is stable only when the various fluorine atoms (or at least halogen atoms) are grouped together. In this respect CH_3CHF_2 is a typical polyfluoride and is stable, while $\text{CH}_2\text{FCH}_2\text{F}$ is better regarded as a double monofluoride and is therefore particularly likely to lose hydrogen fluoride.³⁸ In $\text{CClF}_2\text{CCl}_2\text{F}$ both groups are polyfluorides; it is possible, however, to establish a gradation and show that the inertness of the CClF_2 group is more pronounced than that of the CCl_2F group. For instance, a treatment with aluminum chloride yields $\text{CCl}_3\text{CClF}_2$ in fair yields, before it produces CCl_3CCl_3 .^{69, 70}

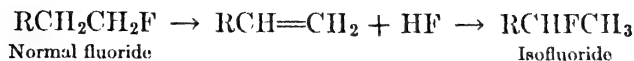
Monofluorides. The instability of the monofluorides, which complicates their preparation, can, however, be turned to advantage in syn-

⁶⁸ Henne and Orchin, unpublished results.

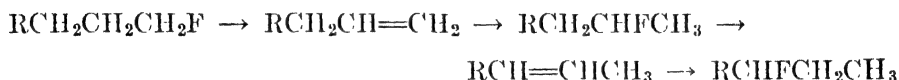
⁶⁹ Henne and Newman, *J. Am. Chem. Soc.*, **60**, 1697 (1938).

⁷⁰ Miller, *ibid.*, **62**, 993 (1940).

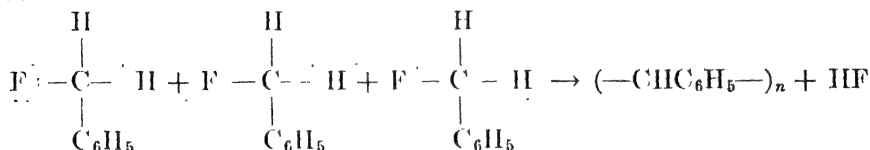
thetic reactions. A primary monofluoride tends to decompose into an olefin and hydrogen fluoride, but since the reaction can be reversed and the recombination occurs in accordance with the rule of Markownikoff, this property leads to isomerization.



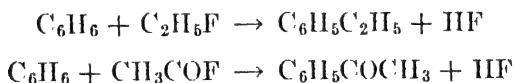
A secondary fluoride loses hydrogen fluoride more readily, and a tertiary fluoride even more so, but recombination does not lead to isomerization. Cyclohexyl fluoride behaves as a typical secondary fluoride. Fluorostearic acid, $\text{CH}_3(\text{CH}_2)_6\text{CHF}(\text{CH}_2)_9\text{CO}_2\text{H}$, and difluorostearic acid, $\text{CH}_3(\text{CH}_2)_6\text{CHFCHF}(\text{CH}_2)_8\text{CO}_2\text{H}$, have, however, been represented as stable compounds. Isomerization by double-bond displacement has also been observed; this is brought about by the same mechanism of successive additions and eliminations:



When hydrogen fluoride cannot be eliminated from two adjacent carbons, it is eliminated by taking one fluorine from one molecule, and one hydrogen from another. This leads to condensation; ^{45, 71} for example:

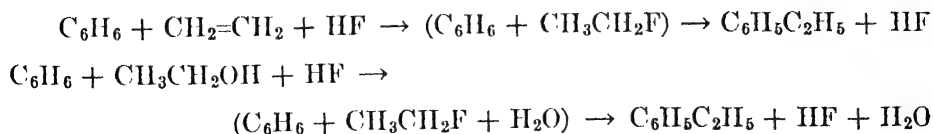


The same elimination may take place between molecules of different compounds, and it also leads to condensation.



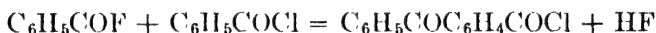
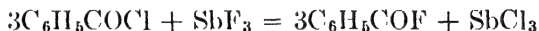
The equivalent of a Friedel-Crafts condensation is therefore obtained, in the absence of aluminum chloride.

One may carry this a step further by forming a monofluoride as an intermediate only.



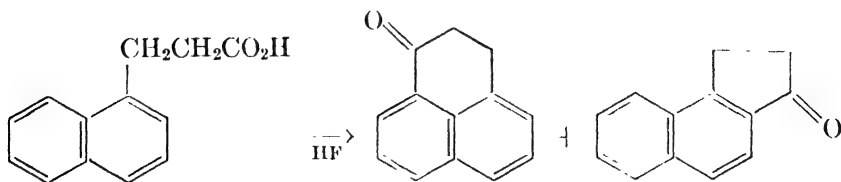
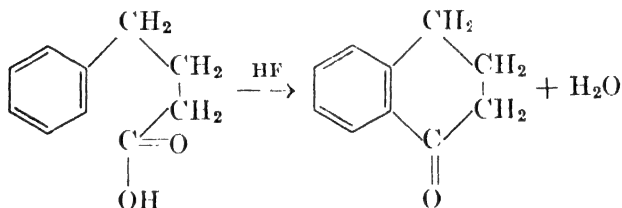
⁷¹ Henne and Leicester, *ibid.*, **60**, 864 (1938).

This mechanism, though not generally accepted, seems particularly well supported by the fact that, in the presence of hydrogen fluoride, benzene and propylene give isopropylbenzene, while benzene and cyclopropane give normal propylbenzene. It is essential that the experimental conditions be controlled to prevent isomerization of the intermediate fluoride, because, otherwise, this isomerization leads to an incorrect interpretation of the reaction mechanism. Additional supporting evidence is the preparation of benzoylbenzoic acid by interaction of benzoyl chloride and antimony fluoride.⁷² In this reaction, all the intermediate products have actually been isolated.



Several cyclizations have been described, which were brought about by hydrogen fluoride.^{73, 74, 75, 76} The hypothesis is here advanced that the mechanism of the reactions is not a mere dehydration but consists in forming an intermediate acyl fluoride, which reacts with the ring compound in typical Friedel-Crafts fashion.

Cyclization of γ -Arylbutyric Acids or β -Arylpropionic Acids.



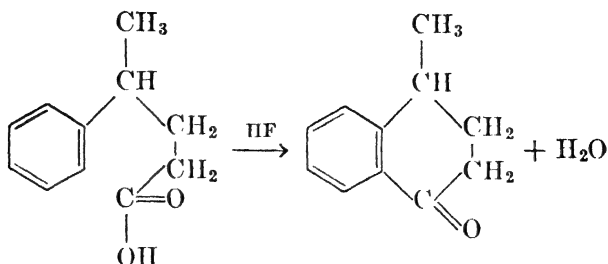
⁷² Voznesenskii, *J. Gen. Chem. (U.S.S.R.)*, **9**, 2148 (1939).

⁷³ Calcott, Tinker, and Weinmayr, *J. Am. Chem. Soc.*, **61**, 949 (1939).

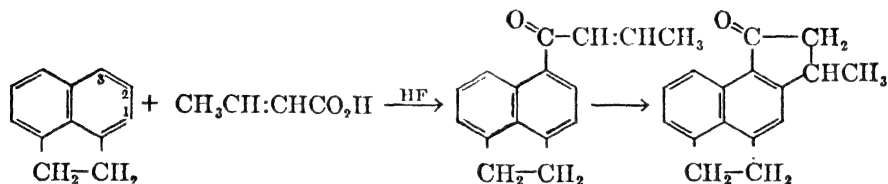
⁷⁴ Fieser and Hershberg, *ibid.*, **61**, 1272 (1939).

⁷⁵ Fieser and Johnson, *ibid.*, **61**, 1647 (1939).

⁷⁶ Fieser and Cason, *ibid.*, **61**, 1740 (1939). See also Fieser and Gates, *ibid.*, **62**, 2333 (1940).

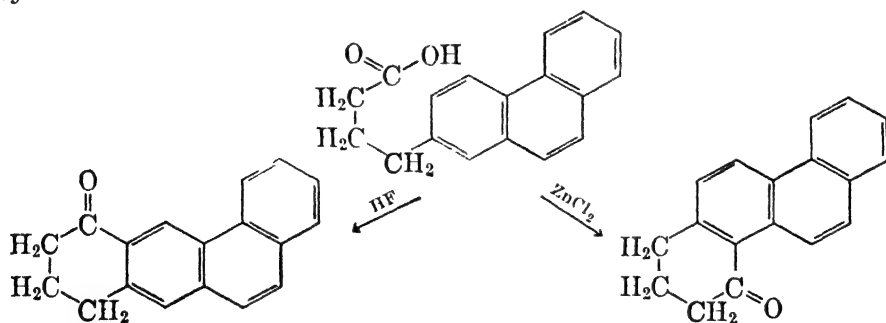


Intermolecular Acylations. In this case, the formation of $\text{CH}_3\text{CH}(\text{F})\text{CH}_2\text{COF}$ as an intermediate is postulated.



When a saturated acid is used, it links to the 1- instead of the 3-position, and the reaction stops when the open-chain ketone is obtained.

Directional Cyclization. The cyclization of γ -(2-phenanthryl) butyric acid, gives a benzanthracene derivative when it is brought about by hydrogen fluoride, while it gives a chrysene derivative when it is caused by zinc chloride.



Polyfluorides. The physiological inertness of the polyfluorides has been illustrated already by dichlorodifluoromethane, CCl_2F_2 . Before being placed on the market as refrigeration agents other chlorofluorides have been thoroughly investigated to establish their lack of toxicity.^{77, 78, 79, 80, 81, 82} Methylene fluoride can be administered in large doses

⁷⁷ "Tests to Show Toxic Irritant and Fire Characteristics of Certain Well-known Refrigerants," Kinetic Chemicals, Inc., Wilmington, Delaware.

⁷⁸ Nuckols, National Board of Fire Underwriters. Miscel. Hazard No. 2375 (1933)

⁷⁹ *Ibid.*, No. 2630 (1935).

⁸⁰ *Ibid.*, No. 2256 (1931).

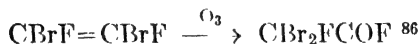
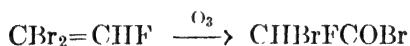
⁸¹ United States Bureau of Mines R. I. 3013.

⁸² Brenner, *J. Pharmacol.*, **59**, 2 (1937).

without ill effect although it is not so thoroughly inert as CCl_2F_2 . Fluoroform is completely inert and has no soporific effect, in complete contrast to chloroform.⁸³

The chemical inertness of the polyfluorides is illustrated by the complete failure to hydrolyze any halogen atom in CCl_2F_2 and by the fact that this fluoride can be passed through molten sodium without causing the metal to tarnish;⁸³ the inertness of the two fluorine atoms is thus shared by the chlorine atoms linked to the same carbon atom. The stabilizing effect of the fluorine extends to halogens linked to a carbon atom once removed; for instance, ethyl iodide is easily hydrolyzed, while a treatment with water and mercuric oxide, in a sealed tube at 140° , for one week, is needed to convert $\text{CHF}_2\text{CH}_2\text{I}$ to difluoroethanol.⁸⁴ Another illustration is the total indifference of the chlorine atoms in CCl_3CF_3 to any treatment involving silver salts or oxides.⁶⁸ The resistance to oxidation is apparent in a comparison of toluene and trifluorotoluene; chromic oxide acts rapidly on toluene to oxidize the side chain and yield benzoic acid, and it leaves the aromatic nucleus intact. Conversely, trifluorotoluene, $\text{C}_6\text{H}_5\text{CF}_3$, resists oxidation much better, but long heating with chromic oxide breaks the ring, to give trifluoroacetic acid in 60 per cent yield.⁸⁵

The resistance to oxidation is apparent even in olefinic derivatives. For example, $\text{CH}_2=\text{CF}_2$ can be mixed with oxygen in a glass container and exposed to sunlight for weeks. After completion of the experiment it can be recovered quantitatively and the glass is not even etched.⁸⁴ By contrast $\text{CH}_2=\text{CCl}_2$ is so unstable that it can hardly be prepared; it polymerizes and oxidizes readily. Intermediate properties are exhibited by $\text{CH}_2=\text{CClF}$. Ozone causes a conversion to acyl halides:



Polyfluoride groups have a marked directing influence. In sharp contrast with CH_3 , a CF_3 side chain is a powerful agent to direct substitution into the *meta* position.⁸⁷ A single fluorine atom in the ring, however, directs a substituent to the *ortho* and *para* positions, and favors *para* over *ortho* replacement.

The chlorination of $\text{CH}_3\text{CF}_2\text{CH}_3$ is a well-defined, stepwise reaction,

⁸³ Midgley and Henne, *Ind. Eng. Chem.*, **22**, 542 (1930).

⁸⁴ Swarts, *Bull. classe sci. Acad. roy. Belg.*, [4] **3**, 383 (1901); [4] **4**, 731 (1902).

⁸⁵ Swarts, *ibid.*, [5] **8**, 343 (1922).

⁸⁶ Swarts, *ibid.*, [3] **36**, 532 (1898).

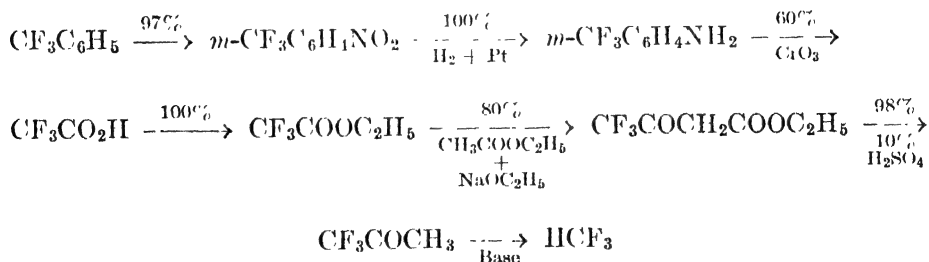
⁸⁷ Swarts, *ibid.*, [5] **6**, 389 (1920).

whose successive steps are $\text{CH}_3\text{CF}_2\text{CH}_2\text{Cl}$, $\text{CH}_3\text{CF}_2\text{CHCl}_2$, $\text{CH}_3\text{CF}_2\text{CCl}_3$, $\text{CH}_2\text{ClCF}_2\text{CCl}_3$, $\text{CHCl}_2\text{CF}_2\text{CCl}_3$, and $\text{CCl}_3\text{CF}_2\text{CCl}_3$. At no stage is there any indication of the presence of the other possible isomer, which is in complete contrast with the chlorination of propane, a completely random reaction.⁴⁰ Similarly, the chlorination of $\text{CF}_3\text{CH}_2\text{CH}_3$ yields successively $\text{CF}_3\text{CH}_2\text{CH}_2\text{Cl} \rightarrow \text{CF}_3\text{CH}_2\text{CHCl}_2 \rightarrow \text{CF}_3\text{CH}_2\text{CHCl}_2 \rightarrow \text{CF}_3\text{CH}_2\text{CCl}_3$, $\text{CF}_3\text{CHClCCl}_3$, and $\text{CF}_3\text{CCl}_2\text{CCl}_3$.²¹

Another effect is that of increasing the acid properties of an adjacent hydroxyl group. Trifluoroacetic acid is a very strong acid, considerably stronger than trichloroacetic acid. Similarly trifluoroethanol and trifluoroisopropyl alcohol show acid properties similar to those of a phenol, and both decompose carbonates and bicarbonates to make a metallic alcoholate. Although it is quite acid difluoroethanol acts only sparingly on a carbonate.^{84, 88, 89}

In general, polyfluoride groups are indifferent to most reagents, and about the only compounds capable of withdrawing the fluorine atoms from the organic molecule are derivatives of aluminum. This is illustrated by the possibility of converting trifluorotoluene to trichlorotoluene by means of aluminum chloride.⁶⁹ More evidence of the stability of the CF_3 group appears in particularly drastic reactions. For instance, the passage of CCl_2F_2 through the electric arc gives rise to CClF_3 and C_2F_6 , while CF_4 gives mostly C_2F_6 , together with C_2F_4 .^{90, 91} Another particularly striking reaction is the preparation of C_2F_6 by electrolysis of trifluoroacetic acid.⁹²

In order to satisfy himself that the properties reported for fluoroform were correct, Swarts undertook, shortly before his death, and successfully completed the following series of reactions. He thereby illustrated the stability of the CF_3 group.^{85, 93, 94}



⁸⁸ Swarts, *Bull. soc. chim. Belg.*, **38**, 99 (1929).

⁸⁹ Swarts, *ibid.*, **43**, 471 (1934).

⁹⁰ Ruff and Bretschneider, *Z. anorg. allgem. Chem.*, **210**, 173 (1933).

⁹¹ Thornton, Burg, and Schlesinger, *J. Am. Chem. Soc.*, **55**, 3177 (1933).

⁹² Swarts, *Bull. classe sci. Acad. roy. Belg.*, [5] **17**, 27 (1931).

⁹³ Swarts, *ibid.*, [5] **12**, 679 (1926).

⁹⁴ Swarts, *ibid.*, [5] **13**, 175 (1927); and private communication.

Relation to Atomic Distances. No single physical property can explain all the chemical effects. However, a consideration of the atomic distances in organic fluorides leads to a remarkable parallelism.

In the methane series, the atomic distances of all the possible chlorides, fluorides, and chlorofluorides have been measured by means of electron diffractions, with the following results.⁹⁵

TABLE VIII
ATOMIC DISTANCES
(In angstrom units)

| | C—F | C—Cl | | C—F | C—Cl |
|---------------------------------------|------|------|--------------------------|------|------|
| CCl ₄ | | 1.76 | CHCl ₃ | | 1.77 |
| CCl ₃ F..... | 1.40 | 1.76 | CHCl ₂ F..... | 1.41 | 1.73 |
| CCl ₂ F ₂ | 1.35 | 1.70 | CHClF ₂ | 1.36 | 1.73 |
| CClF ₃ | 1.35 | 1.70 | CHF ₃ | 1.35 | |
| CF ₄ | 1.36 | | | | |
| CH ₂ Cl ₂ | | 1.77 | CH ₂ Cl..... | | 1.77 |
| CH ₂ ClF..... | 1.40 | 1.76 | CH ₂ F..... | 1.42 | |
| CH ₂ F ₂ | 1.36 | | | | |

In every series it appears that, with the entrance of the second fluorine into the molecules, the carbon-to-fluorine distance is appreciably shortened and, moreover, the carbon-to-chlorine distance is also decreased. This creates a more compact molecule, from which it is considerably more difficult to extract or substitute any constituent part. Although this parallelism is not presented as *the* explanation, it is offered as an important element of it.

PRACTICAL APPLICATIONS

At the time of writing, only polyhalides have been put to wide commercial applications, of which their use as refrigerating agents is by far the most important. Their physiological inertness is particularly valuable in the air-conditioning field, where leakage of the refrigerant into the atmosphere might cause accidents if the compounds were toxic, or might create panics in large audiences if the compounds had a pungent odor, even if the amounts accidentally released were too small to create a real hazard. The fact that the polyfluorides used are chemically stable and are not combustible increases their safety factor.

⁹⁵ Brockway, *J. Phys. Chem.*, **41**, 185 (1937), and sequence.

Another use which is gaining ground is in dyes which bear a polyfluorinated group somewhere in the molecule, because the presence of the fluorine increases the resistance to oxidation and hence prevents fading. The widest present application seems to be the red dye of the official German flag.⁹⁶ It bears a CF_3 group on a naphthyl radical.

The practical use of monofluorides, either as such or as intermediates, is a more recent development, which is just now undergoing semi-scale factory investigation. There seem to be two main applications, petroleum refining and hydrocarbon synthesis.

In petroleum refining, the scheme is to add a small amount of hydrogen fluoride, which causes the highly unsaturated gum-forming hydrocarbons to polymerize or to condense with more saturated ones.⁹⁷ Monofluorides are presumably the intermediate agents; at any rate, the resinous material settles rapidly and can be decanted sooner and more easily than in the customary sulfuric acid refining.

In hydrocarbon synthesis, the scheme consists in causing the equivalent of a Friedel-Crafts condensation, either between an aliphatic and an aromatic derivative, or between two aliphatic compounds. Details of experimental conditions and results are jealously guarded by the industry.

The successful commercialization of fluorides is due to two important industrial developments, a continuous method of manufacturing anhydrous hydrogen fluoride economically and a continuous method of introducing fluorine into organic molecules; both are well surrounded by patents; the features of the second method are substantially as follows:

1. When antimony fluoride is used to introduce fluorine into an organic chloride, it is transformed into antimony chloride; antimony chloride can be acted upon by hydrogen fluoride, to regenerate antimony fluoride and give hydrogen chloride as a by-product.⁹⁸

2. Advantage can easily be taken of the fact that each fluorine substitution lowers the boiling point by some 40° to 50° . If the operation is carried out in a reaction vessel equipped with a dephlegmator, the more volatile fluoride can be allowed to distil off as formed, while the chlorides will reflux back into the reaction chamber, further to be subjected to the source of fluorine.⁹⁹

The combination of these two principles is illustrated in the manufacture of CCl_2F_2 . A reaction vessel, fitted with a dephlegmator, is supplied with a quantity of antimony salt. Hydrogen fluoride and carbon

⁹⁶ Scherer, *Angew. Chem.*, **52**, 457 (1939).

⁹⁷ Kharasch, U. S. pat. 2,076,581 [*C.A.*, **31**, 4104 (1937)].

⁹⁸ Daudt and Youker, U. S. pat. 2,005,705 [*C.A.*, **29**, 5123 (1935)].

⁹⁹ Midgley, Henne, and McNary, U. S. pat. 2,007,208 [*C.A.*, **29**, 5459 (1935)].

tetrachloride are continuously fed into it. The reaction generates CCl_3F , CCl_2F_2 , and HCl , and, if the dephlegmator is properly adjusted, substantial separation of the CCl_2F_2 and HCl from the CCl_4 and CCl_3F is accomplished. The HCl is removed from the discharge of the dephlegmator by passage through water, and after a relatively simple fractional distillation pure CCl_2F_2 is obtained.

ANALYSIS

In general, fluorides are difficult to analyze correctly, except in closed systems. The reason is that the unstable fluorides may lose hydrofluoric acid too easily, while the stable fluorides may escape the field of reaction before they are acted upon.

Gaseous compounds can be analyzed by passage over red-hot silica.^{100, 10} This treatment decomposes the organic compounds to make silicon tetrafluoride, which can be absorbed in an alkaline solution, in which the fluorine ion can be titrated. Liquids or solids can be decomposed with sodium peroxide in a Parr Bomb¹⁰ or with calcium oxide in a tightly closed steel tube brought to red heat.^{43, 101} Other methods are generally cumbersome and inaccurate.

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v. GROSSE, WACKER, and LIND, *J. Phys. Chem.*, **44**, 275 (1940).

¹⁰⁰ Hubbard and Henne, *J. Am. Chem. Soc.*, **56**, 1078 (1934).

¹⁰¹ McNevin and Baxley, *Ind. Eng. Chem., Anal. Ed.*, **12**, 299 (1940).

CHAPTER 12

MOLECULAR REARRANGEMENTS

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INTRODUCTION

Formulas of the molecules of organic compounds which show the arrangement of their constituent atoms are called structural formulas. The methods used in the determination of these structural formulas are based upon certain well-known principles. Often in the application of these fundamental concepts it is necessary to carry out chemical reactions which involve addition, substitution, and the elimination of simple molecules such as nitrogen and water. In such organic reactions it seldom happens that quantitative yields of the desired products are obtained. Side reactions occur, and in many instances the compounds so produced are the main products of the reaction. Two illustrations may be given to show to what extent this may take place: (a) the prepa-

ration of tertiary butyl compounds from isobutyl alcohol and its derivatives; (b) the action of nitrous acid on neopentylamine which produces none of the corresponding alcohol but yields dimethylethylcarbinol. The compounds produced by such "side reactions" are generally the result of rearrangements of the molecules or of their fragments during the reaction process. Therefore, it is of great importance in all phases of organic research to have a knowledge of these rearrangement processes, to study the various mechanisms which have been proposed to account for these changes in order that one may be able to foresee when rearrangements are to be expected, and to know with certainty when they have taken place. Failure to do this has caused the best of investigators to make unfortunate mistakes.

In order to outline definitely the scope of this discussion, and for purposes of greater clarity in what is to be written later, it is to be understood that in this chapter the term "rearrangement" refers to an irreversible reaction which produces a change in the structural arrangement of the molecule with or without the elimination of simple molecules such as water or a hydrogen halide, and which may or may not be unimolecular in its nature. Therefore, subjects such as mutarotation, racemization, Walden inversion, and tautomerism will be omitted. They are essentially reversible processes.

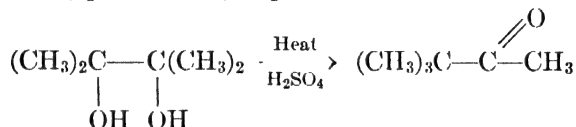
With this definition in mind it is readily seen that transformations of this kind are very common in organic chemistry; in fact, they have been observed ever since Wöhler published his synthesis of urea by a molecular rearrangement of ammonium cyanate. Consequently, it will be impossible in the scope of this chapter to enumerate and to discuss all classes of compounds which undergo a change in the atomic arrangement of their molecules during various reaction processes. In this particular study of the subject a different approach is necessary.

A careful examination of the many hypotheses and theories which have been enunciated to explain the mechanisms of various rearrangement processes shows that most of these explanations can be classified into two groups: (1) Those older interpretations which assume in one form or another the formation of intermediate compounds during the reaction. In these explanations the intermediate compounds which are assumed to be formed vary widely. In some cases they take the form of rings such as cyclopropane and ethylene oxide. In others olefinic compounds are assumed to be the first products of the reaction, and in still others investigators have assumed the intermediate formation of bivalent carbon compounds, etc. (2) Those more recent points of view which would explain all rearrangements on a common basis of free radicals, or of ions, or of an electronic mechanism which does not involve the for-

mation of any intermediate compounds during the rearrangement. It is now the purpose to discuss these more modern points of view and where possible for the purpose of illustration to apply them to various classes of compounds which have been found to undergo rearrangement. For a discussion of the older interpretations the reader is referred to Chapter 8 of the first edition of this treatise.

THE CONCEPT OF THE FORMATION OF FREE RADICALS AND OF IONS AS INTERMEDIATES IN MOLECULAR REARRANGEMENTS

In 1859 Fittig¹ published the results of a series of experiments which he had made in a study of the reducing action of sodium on acetone. The compound pinacol was obtained. In the following year he published a paper which showed that if this substance be heated with sulfuric acid a ketone, pinacolone, is produced.



Numerous examples of this reaction, now known as the pinacol rearrangement, have been found since the time of Fittig's discovery, for not only has the mechanism of the process involved in the rearrangement been the subject of much discussion, but also it has been recognized that in this reaction there is a method for comparing the migrational tendency of different groups, and thereby getting data which will throw light on the problem of affinity distribution in molecules. It is therefore feasible to cite a few typical illustrations to show the extent to which this rearrangement has been studied.

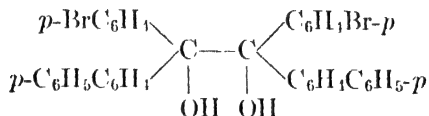
Pinacols of the type $\begin{array}{c} \text{R}_1 \diagup \\ \text{C} - \text{C} \diagup \\ \text{R}_2 \diagdown \quad \text{R}_3 \diagdown \\ | \quad | \\ \text{OH} \quad \text{OH} \\ \text{R}_4 \diagup \end{array}$ have been prepared in which

R_1 , R_2 , R_3 , and R_4 are aliphatic or aromatic groups. Symmetrical pinacols of the aromatic series have been obtained by Gomberg and Bachmann² by a method which involves the use of a mixture of magnesium and magnesium iodide to reduce the ketone. Unsymmetrical pinacols of necessity have to be prepared by other methods. Extensive studies have been made on the rearrangements of these compounds in order to determine the nature of the ketones which are formed. Many

¹ Fittig, *Ann.*, **110**, 23 (1859); **114**, 56 (1860).

² Gomberg and Bachmann, *J. Am. Chem. Soc.*, **49**, 236 (1927).

investigators³ have tried to formulate rules which can be used to predict with some degree of certainty the course of the rearrangement when the four groups are different. Most of these attempts have failed, for the case with which different groups migrate within the molecule is not wholly a property of the group itself, but is dependent to a varying extent on the molecule as a whole. In the symmetrical pinacols of the aromatic series the differences in "migration aptitude" of the groups are more constant. Bachmann and Moser⁴ have made an extensive study of the rearrangement products of certain pinacols of this type. Their results are of special interest, and a summary taken from their paper is listed below. A deduction of the relative "migration aptitude" from the values thus obtained has enabled these investigators to predict with a good degree of accuracy the yields of the ketones which other symmetrical aromatic pinacols should give. Thus, they predicted that the pinacol



upon rearrangement would yield a mixture of ketones showing 6 per cent migration of the *p*-bromophenyl group and 94 per cent migration of the biphenylyl group. In an actual experiment it was found that the rearrangement took place with 4.5 per cent migration of the *p*-bromophenyl group and 95.5 per cent migration of the biphenylyl group. Such results indicate that in the symmetrical pinacols the migration aptitude is dependent to a large extent on the particular group, and not on the molecule as a whole. Studies by other investigators³ have led to a similar conclusion, and lists have been made which arrange the groups in order of decreasing migration aptitude. One such list⁵ goes as follows:

p-anisyl > *p*-tolyl, *p*-biphenylyl, α -naphthyl >

p-isopropylphenyl > *p*-ethylphenyl, *p*-fluorophenyl > phenyl,

p-iodophenyl > $\left\{ \begin{array}{l} p\text{-bromophenyl, } p\text{-chlorophenyl} > o\text{- or } m\text{-chloro- or} \\ \text{bromophenyl, } m\text{-tolyl} > m\text{-anisyl.} \end{array} \right.$

However, it should be noted that as yet no rigid rule can be formulated to predict the extent of the migration of the groups when the pinacol is unsymmetrical. Even in the symmetrical pinacols other factors play

³ See *Ann. Repts. Chem. Soc. (London)*, **27**, 114 (1930), for a review of this subject and for a compilation of references.

⁴ Bachmann and Moser, *J. Am. Chem. Soc.*, **54**, 1124 (1932).

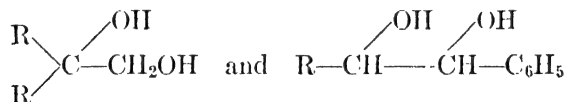
⁵ *Ann. Repts. Chem. Soc. (London)*, **27**, 118 (1930).

MIGRATION OF GROUPS

| Pinacol | Group | Migra- tion | Pinacol | Group | Migra- tion |
|--|---------------------|----------------|--|-------------------------|----------------|
| $\left[\begin{array}{c} p\text{-CH}_3\text{---C}_6\text{H}_4 \\ \text{C}_6\text{H}_5 \\ \text{C} \text{---} \\ \\ \text{OH} \end{array} \right]_2$ | <i>p</i> -Tolyl | 91 | $\left[\begin{array}{c} p\text{-CH}_3\text{---O---C}_6\text{H}_4 \\ \text{C}_6\text{H}_5 \\ \text{C} \text{---} \\ \\ \text{OH} \end{array} \right]_2$ | <i>p</i> -Anisyl | 98 6 |
| | Phenyl | 6 | | Phenyl | 1 4 |
| $\left[\begin{array}{c} p\text{-CH}_3\text{---C}_6\text{H}_4 \\ p\text{-C}_6\text{H}_5\text{---C}_6\text{H}_4 \\ \text{C} \text{---} \\ \\ \text{OH} \end{array} \right]_2$ | <i>p</i> -Tolyl | 57 | $\left[\begin{array}{c} p\text{-CH}_3\text{---O---C}_6\text{H}_4 \\ p\text{-CH}_3\text{---C}_6\text{H}_4 \\ \text{C} \text{---} \\ \\ \text{OH} \end{array} \right]_2$ | <i>p</i> -Anisyl | 96 7 |
| | <i>p</i> -Bi-phenyl | 43 | | <i>p</i> -Tolyl | 3 3 |
| $\left[\begin{array}{c} m\text{-CH}_3\text{---C}_6\text{H}_4 \\ \text{C}_6\text{H}_5 \\ \text{C} \text{---} \\ \\ \text{OH} \end{array} \right]_2$ | <i>m</i> -Tolyl | 66 | $\left[\begin{array}{c} p\text{-CH}_3\text{---O---C}_6\text{H}_4 \\ p\text{-C}_6\text{H}_5\text{---C}_6\text{H}_4 \\ \text{C} \text{---} \\ \\ \text{OH} \end{array} \right]_2$ | <i>p</i> -Anisyl | 96 8 |
| | Phenyl | 34 | | <i>p</i> -Bi-phenyl | 3 2 |
| $\left[\begin{array}{c} m\text{-CH}_3\text{---C}_6\text{H}_4 \\ p\text{-C}_6\text{H}_5\text{---C}_6\text{H}_4 \\ \text{C} \text{---} \\ \\ \text{OH} \end{array} \right]_2$ | <i>m</i> -Tolyl | 13 | $\left[\begin{array}{c} p\text{-CH}_3\text{---C}_6\text{H}_4 \\ p\text{-CH}_3\text{---C}_6\text{H}_4 \\ \text{C} \text{---} \\ \\ \text{OH} \end{array} \right]_2$ | <i>p</i> -Tolyl | 82 |
| | <i>p</i> -Bi-phenyl | 87 | | <i>p</i> -Chloro-phenyl | ? |

an important role in the rearrangement of the groups. For instance, Bachmann and Sternberger⁶ have shown that when the biphenylene group is present the order and the extent of migration are reversed to those in the above table, and when unsymmetrical pinacols are studied the results⁷ show no simple relationships. Therefore, it is evident that more data are necessary before all factors which govern the extent of these changes are known.

The pinacol rearrangement also takes place in other classes of glycols. Compounds of the type



have been prepared. These molecules undergo rearrangement under varying conditions. For example, 2-methylpropanediol-1,2,⁸

$\begin{array}{c} \text{OH} \\ \diagup \\ (\text{CH}_3)_2\text{C} \text{---} \text{CH}_2\text{OH} \end{array}$, gives isobutyric aldehyde, $(\text{CH}_3)_2\text{CH} \text{---} \text{CHO}$, when heated with water at 180–200° in a sealed tube. When hydrobenzoin,⁹

⁶ Bachmann and Sternberger, *J. Am. Chem. Soc.*, **55**, 3821 (1933).

⁷ Bachmann and Sternberger, *ibid.*, **56**, 170 (1934).

⁸ Nevole, *Ber.*, **9**, 448 (1876).

⁹ Breuer and Zincke, *Ann.*, **198**, 141 (1879).

$\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{CH}(\text{OH})\text{C}_6\text{H}_5$, is warmed with sulfuric acid, diphenylacetaldehyde, $(\text{C}_6\text{H}_5)_2\text{CH}-\text{C}(=\text{O})\text{H}$, is obtained in good yield. Compounds of the

type $\begin{array}{c} \text{R}_1 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{R}_2 \end{array} \begin{array}{c} \text{OH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{H} \end{array} - \text{C}(=\text{O})\text{H}$ also give rearrangement products. Danilov¹⁰ has shown that, when an alcoholic solution of benzilic aldehyde,

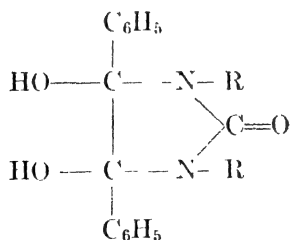
$(\text{C}_6\text{H}_5)_2\text{C}(\text{OH})\text{CHO}$, is warmed with a small amount of sulfuric acid, benzoin, $\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{CH}(\text{OH})\text{C}_6\text{H}_5$, is produced. Semi-pinacols¹¹ undergo this type of rearrangement. Thus 1-phenyl-2-propylpentanediol-1,2,

$\text{C}_6\text{H}_5\text{CH}(\text{OH})\text{CH}(\text{OH})\text{C}_3\text{H}_7$, in the presence of cold sulfuric acid gives

5-phenyloctanone-4, $\begin{array}{c} \text{C}_6\text{H}_5 \\ \diagdown \\ \text{CH} \\ \diagup \\ \text{C}_3\text{H}_7 \end{array} \text{CH}(\text{OH})\text{C}_3\text{H}_7$. If, however, hot dilute sulfuric acid is used as the rearranging agent a semi-hydrobenzoin

change occurs, and phenyldi-*n*-propylacetaldehyde, $\begin{array}{c} \text{C}_6\text{H}_5 \\ \diagdown \\ \text{C} \\ \diagup \\ \text{C}_3\text{H}_7 \end{array} - \text{C}(=\text{O})\text{H}$, is

formed. It should also be pointed out that this pinacol type of rearrangement is not necessarily confined to straight-chain compounds. In a study of the condensation which takes place between urea, or substituted ureas, and benzil Biltz¹² has prepared cyclic compounds of the following type and has found that they undergo rearrangement in

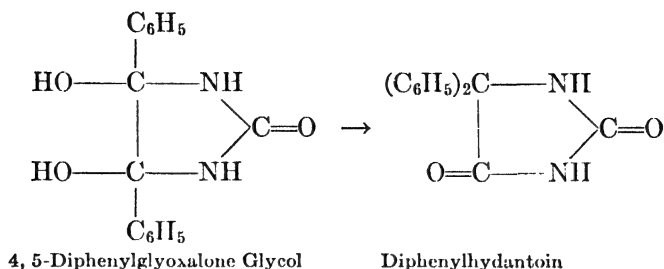


the presence of sodium hydroxide. For example, 4,5-diphenylglyoxal glycol gives diphenylhydantoin:

¹⁰ Danilov, *Ber.*, **60**, 2390 (1927).

¹¹ Tiffeneau and Levy, *Bull. soc. chim.*, [4] **33**, 735 (1923).

¹² Biltz, *Ber.*, **41**, 1385 (1908).



Many other examples¹³ of this type of rearrangement in cyclic compounds are known, but the underlying principles involved are essentially the same.

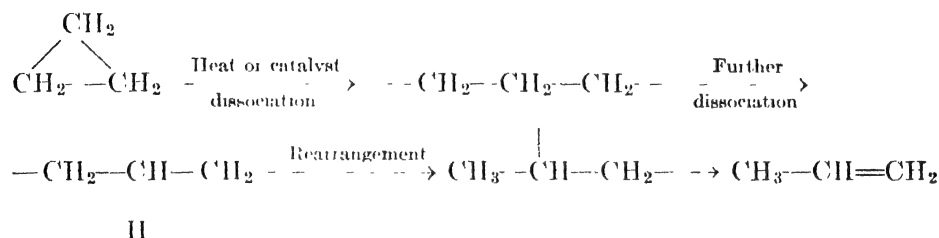
These few typical illustrations of the pinacol rearrangement have been given not only to show how very common conversions of this kind are in organic chemistry, and to what extent they have been studied, but also to show how important it is that chemists have an understanding of the mechanism of the processes by means of which such rearrangements take place. Many reactions which at first sight seem to be very different are found in reality to be very similar in their nature and can be grouped together and explained on the basis of a common mechanism.

A survey of the literature shows that in the hypotheses which were first put forward to explain rearrangements of this type attempts were made to avoid the assumption that atoms and groups within a molecule can undergo a direct interchange. Investigators in this field preferred to assume that such reactions involve the formation of relatively stable intermediate compounds. As stated in the introduction these compounds take the form of cyclic rings. For this particular rearrangement, cyclobutane and ethylene oxide intermediates were assumed. For other types of rearrangements cyclopropane derivatives and olefins were postulated. As further studies were made, however, on compounds which undergo these irreversible reactions involving a change in the structural arrangement of the molecule, facts were found in abundance which clearly showed the fallacy of this basic idea and the dangers involved in making such efforts. As a consequence of the limited applicability of such concepts there has emerged the fact that "step by step" mechanisms of these types cannot be used to formulate changes which so often take place within the molecule itself and which are intramolecular in their nature. Therefore, it is not surprising to find that investigators have adopted a different view and that as a result hypotheses of a different type have been formulated.

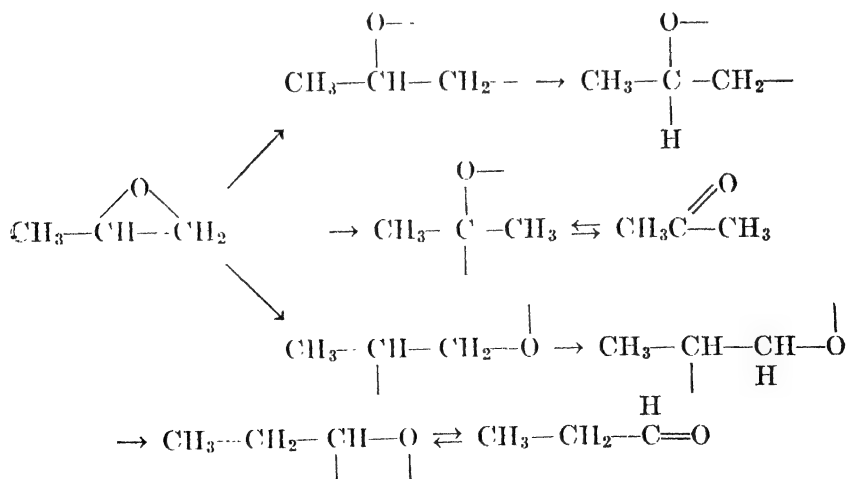
¹³ Meerwein, *Ann.*, **396**, 211 (1913). See also, Porter, "Molecular Rearrangements," Chemical Catalog Co., New York (1928).

The theoretical and experimental investigations of Nef ¹⁴ contributed greatly to this change in ideas. It is now recognized that the chemistry of bivalent and trivalent carbon plays an important role in many fundamental reactions of organic chemistry. Applications of these concepts have been made to the reaction mechanisms involved in molecular rearrangements, and today it is found that many theories have been advanced which in one form or another assume dissociation of a molecule into fragments.

Nef was the first to explain rearrangements on this basis. Cyclopropane may serve as an example. It is to be recalled that when this compound is heated in contact with certain catalytic agents propylene is formed. A dissociation into active molecules containing free valences is first assumed to take place. In this active state migration of a hydrogen atom occurs, and propylene is produced. Nef formulated the various steps as follows:



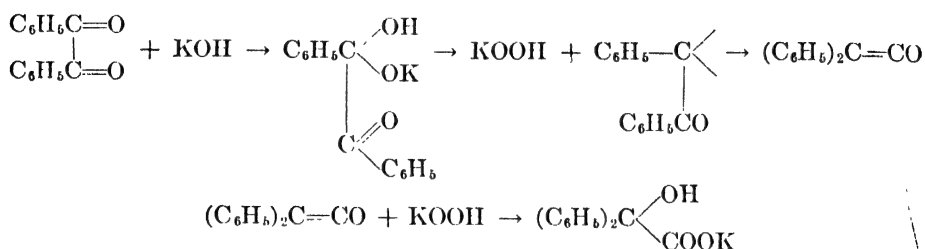
He advanced a similar mechanism to explain the rearrangement of propylene oxide into acetone and propionaldehyde.



¹⁴ For compilation of references consult Henrich, "Theories of Organic Chemistry," translation by Johnson and Hahn, John Wiley & Sons, New York (1922), Chapter XIV

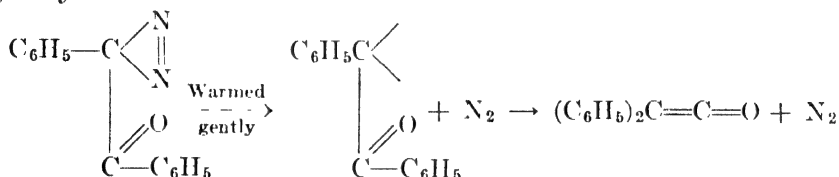
Since no detectable amount of vinyl methyl ether is formed in the rearrangement it was concluded that a dissociation involving a cleavage of the carbon-carbon bond did not take place.

Nef also assumed predissociation in his mechanism for the benzilic acid rearrangement.¹⁵ Although his particular formulation has had to be abandoned because of facts subsequently discovered, Schroeter¹⁶ has proposed the following modification:

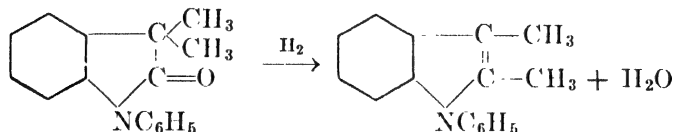


According to this formulation diphenylketene is the intermediate product during the reaction.

Schroeter and Wachendorf¹⁶ found evidence for this mechanism in the fact that they succeeded in preparing diphenylketene from azibenzil in good yield.



It is of interest to note that this concept has been used to explain other types of molecular rearrangements. Instances are known in the indole derivatives, and in the pyrazoles where a methyl group transfers its position from a carbon atom to another carbon atom during reduction processes. Brunner¹⁷ has reported that 1-phenyl-3,3-dimethyloxindole yields 1-phenyl-2,3-dimethylindole when reduction is carried out under suitable conditions.



Again, Knorr¹⁸ has shown that 1-phenyl-3,4,4-trimethylpyrazolone

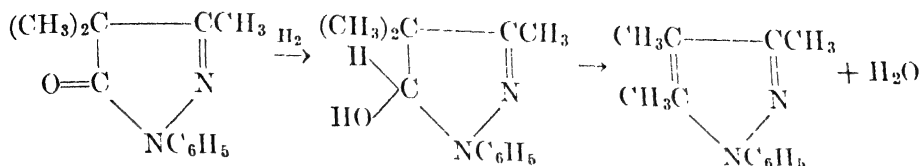
¹⁵ Nef, *Ann.*, **298**, 372 (1897); **335**, 272 (1904).

¹⁶ Schroeter and Wachendorf, *Ber.*, **42**, 2336, 2339, 3361 (1909).

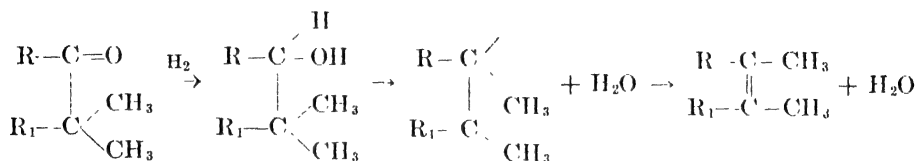
¹⁷ Brunner, *Monatsh.*, **21**, 179 (1900).

¹⁸ Knorr, *Ber.*, **36**, 1272 (1903).

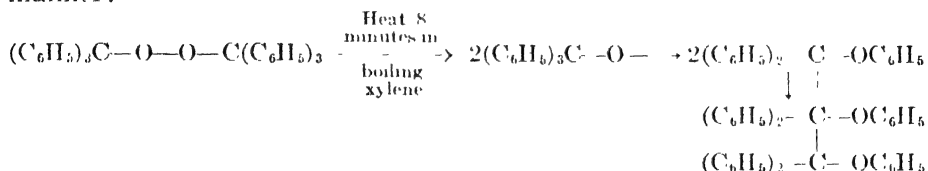
on reduction with sodium and alcohol yields 1-phenyl-3,4,4-trimethyl-5-oxy-pyrazolone, which when treated with mineral acids produces 1-phenyl-3,4,5-trimethylpyrazole.



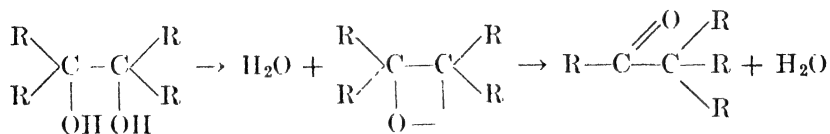
Other reactions are known and are discussed by him, and for them all Knorr has proposed the following mechanism.



In this connection the rearrangement of triarylmethyl peroxides is of interest. Wieland¹⁹ has formulated the process in the following manner:



It remained for Tiffeneau and his colleagues²⁰ to apply this concept to the pinacol and allied rearrangements. After extensive experimental studies these investigators came to the conclusion that a mechanism based on dissociation into active molecules with free valences best explained this type of change and that loss of water preceded the rearrangement. According to them the pinacol rearrangement is to be formulated as follows:

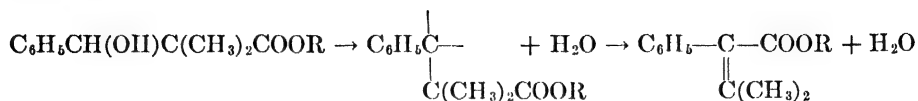


It is Tiffeneau's²⁰ belief that in all rearrangements which involve the elimination of simple molecules such as water and nitrogen, and are truly intramolecular in their nature, a dissociation into "intermediate

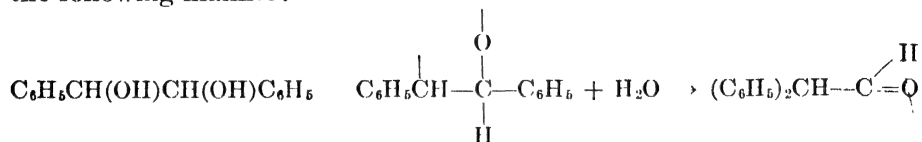
¹⁹ Wieland, *Ber.*, **44**, 2250 (1911).

²⁰ Tiffeneau, *Rev. gén. sci.*, **18**, 583 (1907); *Bull. soc. chim.*, [4] **1**, 1221 (1907); *Compt rend.*, **143**, 684 (1906).

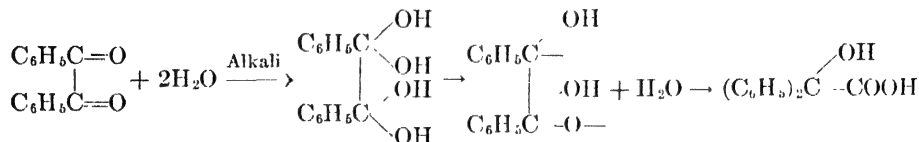
systems which possess free valences" first takes place, instead of intermediate compounds with saturated valences which are more or less structurally stable. Thus the rearrangement of phenylhydroxypivalic acid ester which involves a migration of the carbalkoxyl group is formulated as follows:



The transformation of glycols such as hydrobenzoin is represented in the following manner:



The mechanism for the benzilic acid rearrangement becomes:



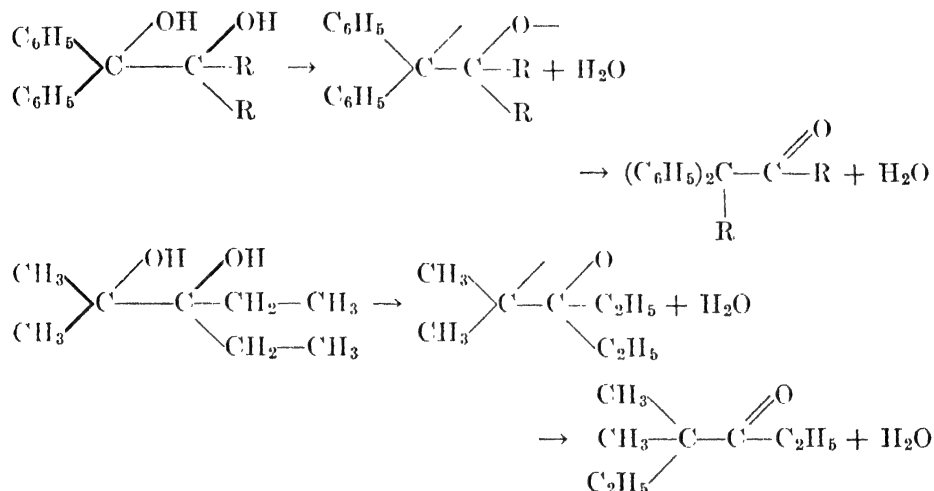
Tiffeneau also assumes the intermediate formation of active molecules with free valences in the rearrangement of methylaniline into *p*-toluidine; of *N*-alkyl- and *N*-acylpyrroles into *C*-alkyl- and *C*-acylpyrroles; of phenylhydroxylamine into *p*-aminophenol; of hydrazobenzene into benzidine, etc. He has also applied his mechanism to rearrangements in the camphor derivatives.

Essentially the same conclusions have been reached by Montagne²¹ and by Meerwein^{13, 22} in their experimental studies of the pinacol rearrangement. They have also shown that cyclic compounds are not found as intermediates. Meerwein and his co-workers believe with Tiffeneau that in these rearrangements the change is caused by a direct loss of water from the pinacol, and subsequent migration of a radical. As they have pointed out, it makes no difference in the symmetrical glycols which hydroxyl group is eliminated; but with unsymmetrical glycols different products can be formed depending on the hydroxyl group which is removed. Obviously, in general, the less firmly attached group will be mainly eliminated, and from the nature of the ketone which is formed the relative bond strength of the hydroxyl groups can be determined.

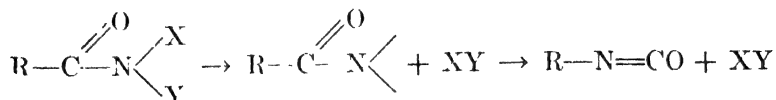
²¹ Montagne, *Rev. gén. sci.*, **18**, 591 (1907); *Ber.*, **51**, 1482 (1918).

²² Meerwein, *Ann.*, **419**, 121 (1919).

Using this approach to the problem Meerwein obtained data on the affinity of groups in these pinacols. The phenyl group greatly increases the reactivity of the adjoining hydroxyl group. In the aliphatic series he finds that the "valence requirements" of the normal alkyl groups diminish with increasing number of carbon atoms, but that this is not continuous; the alkyl groups with an odd number of carbon atoms have greater affinity than those with an even number of carbon atoms. Using light and heavy lines for the bonds he has formulated the reaction as follows:



This concept of the intermediate formation of molecules with free valences has been advanced to explain the mechanism of the Curtius, Hofmann, and Lossen rearrangements. Tiemann²³ first suggested that an unstable univalent nitrogen derivative is formed as an intermediate in the conversion of benzhydroxamic acid, $\text{C}_6\text{H}_5\text{CONH(OH)}$, into aniline and carbon dioxide. In a series of extensive investigations on halogen amides, RCONHBr , acyl azides, RCON_3 , and hydroxamic acids, RCONH(OH) , Stieglitz and his students²⁴ developed this suggestion and made it evident that the Curtius, Hofmann, and Lossen rearrangements are fundamentally alike. Stieglitz proposed that the mechanism be formulated as follows:



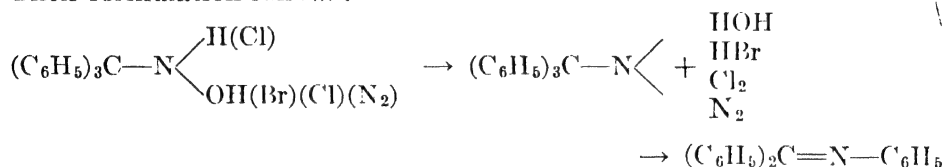
The isocyanate which is formed then reacts with water to produce

²³ Tiemann, *Ber.*, **24**, 4163 (1891).

²⁴ For a compilation of references see Porter, "Molecular Rearrangements," Chemical Catalog Co., New York (1928), p. 16.

amines, and with alcohol or phenol to give urethanes. The action of amines on the isocyanates yields the substituted ureas. Focusing their attention on the effect of the groups X and Y these investigators also demonstrated that transformations of this kind take place in other nitrogen compounds, and that one can expect rearrangements when X and Y are of such a nature that they can be removed as simple molecules such as water, nitrogen, halogens, and hydrogen halides. A few examples will serve to illustrate this point.

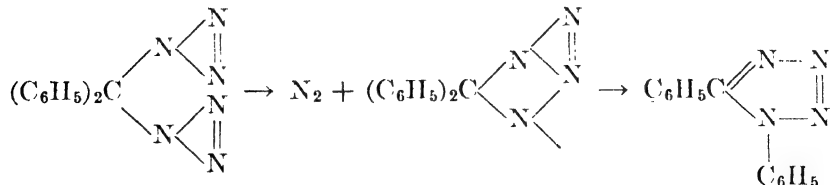
Triphenylmethylhydroxylamine and its related compounds have been found to undergo rearrangement. Stieglitz and his students have shown that the hydroxylamine, haloamine, dichloroamine, and azide rearrange to give the same product—the phenylimide of benzophenone.²⁵ Their formulation follows:



It is also known that an alkyl group may be substituted for a phenyl group. Methyl diphenylmethyl dichloroamine,²⁶ $(\text{C}_6\text{H}_5)_2\text{C}(\text{CH}_3) \left(\text{N} \begin{array}{l} \nearrow \text{Cl} \\ \searrow \text{Cl} \end{array} \right)$, yields the phenylimide of acetophenone.

This last reaction is of interest in that it shows the migrational aptitude of a methyl group as compared to a phenyl group. Other studies of this nature have been made on these compounds. Morgan²⁷ has observed that substitution of a halogen in the benzene nucleus of triphenylmethylhydroxylamine has little effect on the migrational aptitude. Three products in relatively equal amounts are formed when *p*-bromophenyl-*p*-chlorophenyl-phenylmethylchloroamine undergoes rearrangement.

Schroeter¹⁶ has used this mechanism to explain the formation of tetrazoles from diazides.

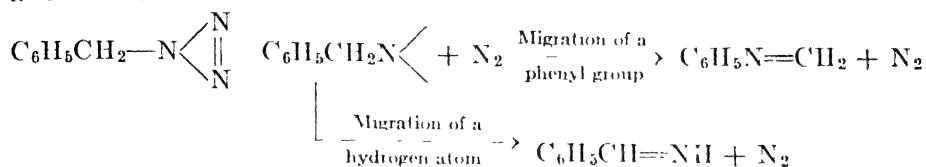


²⁵ Stieglitz and Vosburgh, *Ber.*, **46**, 2151 (1913), Vosburgh, *J. Am. Chem. Soc.*, **38**, 2081 (1916); Stieglitz and Leech, *Ber.*, **46**, 2147 (1913), *J. Am. Chem. Soc.*, **36**, 272 (1914); Senior, *ibid.*, **38**, 2718 (1916).

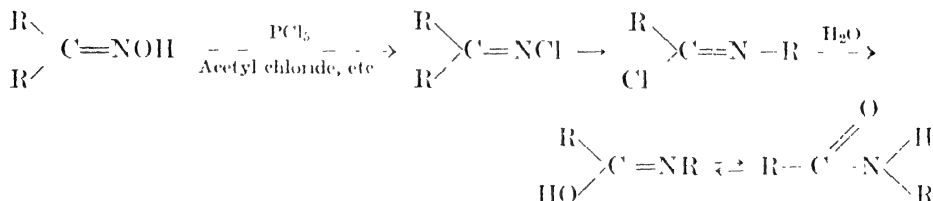
²⁶ Neff, Thesis, University of Chicago (1927) [*C. A.*, **22**, 3639 (1928)].

²⁷ Morgan, *J. Am. Chem. Soc.*, **38**, 2095 (1916).

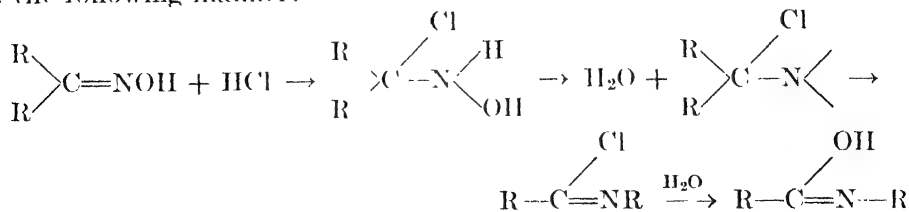
Curtius²⁸ has shown that benzylazide yields methylene aniline on rearrangement. Benzylideneimide is obtained as a by-product. On the basis of the mechanism of Stieglitz the reaction is to be formulated as follows:



Stieglitz²⁴ used this concept to explain the Beckmann rearrangement of oximes into amides. This reaction takes place when an oxime is treated with such reagents as phosphorus pentachloride, phosphorus oxychloride, or acetyl chloride. Hantzsch²⁹ had previously proposed that a chlorimidoketone was formed as an intermediate compound in this rearrangement.



Stieglitz and Peterson³⁰ examined this mechanism by preparing several chlorimidoketones and studying their chemical properties. They found that these compounds did not rearrange under the conditions which bring about the conversion of oximes into amides, and from their results they were compelled to conclude that they were not formed as intermediates during the rearrangement process. A mechanism was then proposed which assumed the intermediate formation of a univalent nitrogen compound, thereby placing this rearrangement on a common basis with those changes of the Curtius, Hofmann, and Lossen types. According to them the first step in the process involves an addition of hydrogen chloride to the oxime. Loss of a molecule of water produces the univalent nitrogen derivative. They formulated their mechanism in the following manner:



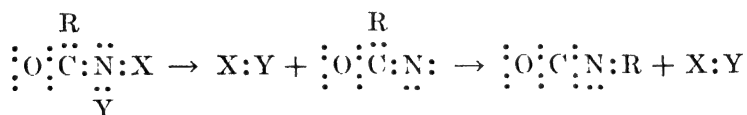
²⁸ Curtius and Darapsky, *J. prakt. Chem.*, [2] **63**, 428 (1901); *Ber.*, **35**, 3229 (1902)

²⁹ Hantzsch, *Ber.*, **35**, 3579 (1902).

³⁰ Stieglitz and Peterson, *Ber.*, **43**, 782 (1910); Peterson, *Am. Chem. J.*, **46**, 325 (1911)

From the illustrations which have been given it can be seen that this concept of the intermediate formation of active molecules with free valences has found widespread use. However, the application of this view to experimental facts which have been obtained since the idea was proposed reveals the fact that frequently its employment is open to criticism. For example, Nicolet and Pele³¹ have criticized Schroeter's interpretation of the benzilic acid rearrangement which postulates the intermediate formation of a bivalent carbon compound, and of diphenylketene. They state that this theory involves the assumption that in the presence of hydroxylic solvents diphenylketene will add the potassium salt of hydrogen peroxide to give benzilic acid more rapidly than it adds water or alcohol. From their experimental results they are forced to conclude that this is not the fact. However, they are careful to point out that their work does not show the impossibility of active molecules with free valences. It is only with Schroeter's application of the concept that they are in disagreement.

The concept does not take into account certain factors which have a pronounced effect on the tendency of molecules to undergo rearrangement. In their studies of the Curtius, Hofmann, and Lossen rearrangements, Jones and students^{32a} have shown that the ease of such transformations does not depend solely on the nature of the groups X and Y. Jones and Hurd^{32b} made a comparative study of the rearrangement of monophenyl-, diphenyl-, and triphenylacethydroxamic acids and their derivatives. They found that the ease of rearrangement was greatest with the derivatives of triphenylacethydroxamic acid. The derivatives of monophenylacethydroxamic acid showed the least tendency to give rearrangement products. On the basis of their results they suggested an interpretation of these reactions based upon the electronic conception of the chemical bond, and they put forward the generalization that "the ease of rearrangement is dependent upon the tendency of the radical R in the univalent nitrogen derivatives to exist as a free radical." Their formulation which excluded the oximes is as follows:



Evidence in support of this hypothesis has been submitted by Jones and Root.^{32a} These investigators studied hydroxamic acids which are

³¹ Nicolet and Pele, *J. Am. Chem. Soc.*, **43**, 935 (1921).

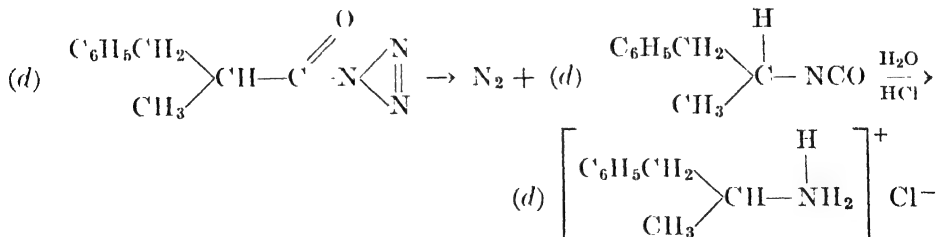
³² (a) Jones and Neuffer, *ibid.*, **39**, 659 (1917); Jones and Warner, *ibid.*, **39**, 413 (1917); Jones and Wallis, *ibid.*, **48**, 169 (1926); Jones and Root, *ibid.*, **48**, 181 (1926); Jones and Mason, *ibid.*, **49**, 2528 (1927); Dougherty and Jones, *ibid.*, **46**, 1535 (1924). (b) Jones and Hurd, *ibid.*, **43**, 2422 (1921).

isomeric with triphenylacethydroxamic acid. *o*- and *p*-Benzhydrylbenzhydroxamic acids were prepared. In both these compounds they found that rearrangement of their derivatives does not occur at temperatures at which the isomeric triphenylmethyl compound rearranges. Thus, the ease of rearrangement depends upon the electronegativity of the groups fastened to the central carbon atom of the radical.

Hurd ³³ has prepared certain derivatives of N,N-diphenyl-N'-hydroxyurea, $(C_6H_5)_2N-C(=O)-NHOH$, and has found that they give rearrangement products, but that the change does not occur in the corresponding N-monophenyl derivatives.

The mechanism by means of which the R group originally attached to the carbon atom, migrates to the nitrogen atom has been the subject of much discussion. Its electronic nature has been given different interpretations. It is generally accepted that in these rearrangements a shift of an electron pair takes place from the carbon atom to the nitrogen atom. Jones ³⁴ considered the group to be of the nature of a positive radical. In this interpretation the electron pair and the group held by it do not migrate together. Jones and Hurd ^{32b} assumed that during the rearrangement the radical exists momentarily as a free radical. Stieglitz ³⁵ has postulated that the group is essentially a negative radical, and that during such rearrangements the electron pair with its group shifts from the carbon atom to the nitrogen atom.

In an attempt to gain further insight into the mechanism of such rearrangement processes Jones and Wallis ^{32a} studied the nature of the products formed when the radical, R, contains an asymmetric carbon atom. They found that *d*-benzylmethylacetazide rearranges readily to produce an optically active isocyanate which on hydrolysis gives an optically active amine hydrochloride.



Similar rearrangements have been carried out on the corresponding optically active amide, and hydroxamic acid. From these experiments the fact has emerged that not only are the products optically active in

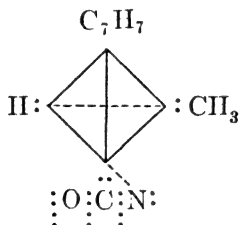
³³ Hurd, *J. Am. Chem. Soc.*, **45**, 1472 (1923).

³⁴ Jones, *Am. Chem. J.*, **50**, 441 (1913).

³⁵ Stieglitz and Leech, *J. Am. Chem. Soc.*, **36**, 280 (1914); Stieglitz and Stagner, *ibid.*, **38**, 2047 (1916). Stieglitz and co-workers, *Proc. Natl. Acad. Sci. U. S.*, **1**, 207 (1915).

all three cases, but the value of the rotatory power of the amine hydrochloride formed in the rearrangements is the same. This strongly indicates that during the reaction partial racemization does not take place. The conditions used in the three experiments are very different, and it is highly improbable that the same degree of racemization would occur. Any interpretations of the electronic nature of the radical during the reaction process must explain this fact.

In the discussion of their experiments, Jones and Wallis^{32a} suggested two possible interpretations. (a) The group migrates as a positive radical, and is of the nature of a carbonium ion. This is essentially an ionic hypothesis and the interpretation is suggested by the fact that there are many reactions in which substitution on an asymmetric carbon atom does not lead to racemization. It implies that a positive charge may play the part of a fourth group in maintaining asymmetry, an idea first enunciated by Biilmann³⁶ to explain the action of the silver ion on *d*- α -bromopropionic acid, and more recently used by McKenzie and co-workers³⁷ to explain the experimental results obtained by them in their study of the rearrangements of certain amino alcohols. It will be shown subsequently that there are serious objections to this idea. (b) The rearranging group does not exist either as a positive, negative, or neutral free radical but "in some way before the group actually parts company with its carbon neighbor, the univalent nitrogen atom has begun already to exercise its influence on the radical in such a manner that when cleavage actually does take place a change in the configuration of the groups about the asymmetric carbon atom is prevented." They imagined this influence to be of the nature of a partial valence and pictured the univalent nitrogen derivative in the following manner:



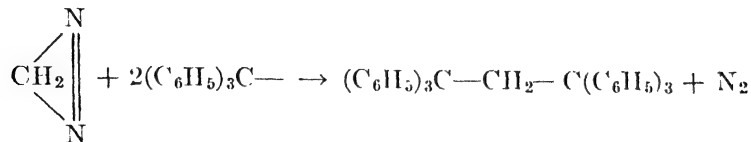
This interpretation implies that in molecular rearrangements which are intramolecular in nature the rearranging group is at no time actually free and unattached. From this viewpoint, the work of Wieland on the occurrence of free radicals in chemical reactions is of interest. Other facts recorded in the chemical literature substantiate this view.

It is well known that triphenylmethyl is an excellent reagent for the

³⁶ Biilmann, *Ann.*, **388**, 330 (1912).

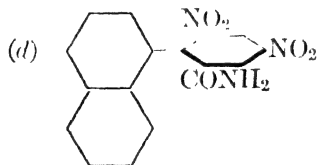
³⁷ McKenzie, Roger, and Wills, *J. Chem. Soc.*, 779 (1926).

detection of free radicals. For example, Wieland³⁸ has used it in his experiments on tetraphenylhydrazine. Schlenk³⁹ has shown that when diazomethane is allowed to decompose under suitable conditions in the presence of triphenylmethyl the formation of ethylene is prevented.



With these facts in mind Wallis⁴⁰ studied the nature of the products formed in certain molecular rearrangements when the reactions were carried out in the presence of free radicals. In the absence of this highly unsaturated compound, benzylmethylacetazide rearranges quantitatively to give benzylmethylmethyl isocyanate.^{37a} If this same reaction is allowed to take place in the presence of triphenylmethyl it can be readily seen that if the rearranging group in its migration from the carbon atom to the nitrogen atom exists as a free radical the formation of two isocyanates is possible. It would be expected also that, if a univalent nitrogen compound were formed as an intermediate, an addition compound with triphenylmethyl would result. But this is not the fact. When a benzene solution of benzylmethylacetazide is allowed to rearrange in the absence of oxygen in a benzene solution of triphenylmethyl only one isocyanate is produced. No additional compounds with univalent nitrogen derivatives are formed in detectable amounts. A quantitative determination of the amount of oxygen absorbed by the free radical remaining after the rearrangement also shows that none of it takes part in the rearrangement.

Further evidence in support of this view has been obtained by Wallis and Moyer,⁴¹ who studied the Hofmann rearrangement of *d*-3, 5-dinitro-



6- α -naphthylbenzamide. The conversion was brought about in the usual manner by the action of sodium hypobromite. The amine so obtained was found to be optically active.

It is to be noted that in this molecule optical activity is due to molecular asymmetry conditioned by the restriction of free rotation about the

³⁸ Wieland, "Die Hydrazine," Enke, Stuttgart, 1913.

³⁹ Schmidlin, "Das Triphenylmethyl," Enke, Stuttgart, 1914 (Investigator Schlenk).

⁴⁰ Wallis, *J. Am. Chem. Soc.*, **51**, 2982 (1929).

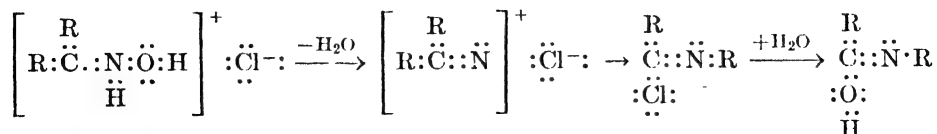
⁴¹ Wallis and Moyer, *ibid.*, **55**, 2598 (1933).

axial bond. The rearrangement takes place with no change in sign of the rotatory power, and in such a manner as to produce no detectable racemization. The results show that migration of the rearranging group is not possible in any free form, either as a positive, negative, or neutral radical, for, if it were at any time free, rotation about the biphenyl linkage would be possible, and an inactive or at least a partially racemized product would have been obtained.

These experiments make it evident that in these types of molecular rearrangements intramolecular processes are being dealt with. The concept of the intermediate formation of free radicals or ions does not explain all the facts because such changes often involve a transference of electrons within the molecule itself. For this reason it would seem that such rearrangements should be best explained on the basis of an electronic mechanism. But before this latter theory is considered it is important that mention be made of certain other criticisms which have been leveled against a universal use of the concept now under discussion.

Montagne ⁴² has criticized Stieglitz's ^{24, 25, 30} application of this interpretation to the Beckmann rearrangement of oximes. He points out that the addition of hydrogen halides to the oxime as assumed by Stieglitz breaks the double bond and thereby destroys geometrical isomerism since there is no longer restricted rotation between the carbon atom and the nitrogen atom. Under these conditions the same intermediate compound would be produced from the two geometrical isomers, and identical rearrangement products would be expected to be obtained. This is known to be contrary to fact.

Stieglitz has revised his formulation of the mechanism of this change to meet this criticism. It has been shown by Schroeter ⁴³ and by Henrich ⁴⁴ that the hydrogen halide addition products of oximes are salts, and that only those oximes which form salts undergo the Beckmann rearrangement. In his revised formulation Stieglitz writes these oxime salts as substituted ammonium salts. Loss of water and rearrangement take place within the substituted ammonium ion. In terms of the electronic conception of the chemical bond his ideas may be formulated in the following manner:



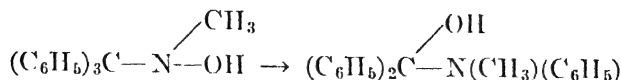
It has also been necessary to modify the concept of the intermediate

⁴² Montagne, *Ber.*, **43**, 2014 (1910).

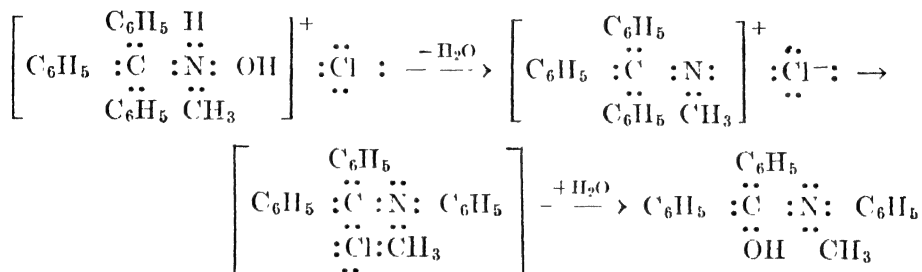
⁴³ Schroeter, *Ber.*, **44**, 1205 (1911).

⁴⁴ Henrich, *Ber.*, **44**, 1533 (1911).

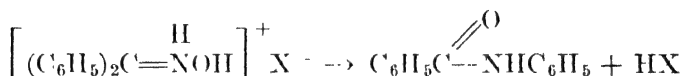
formation of an univalent nitrogen derivative in order to explain the rearrangement of N-triphenylmethyl-N-methylhydroxylamine:³⁵



Here, it is not possible to form an intermediate univalent nitrogen compound in the sense in which it was originally used to explain these rearrangements. Stieglitz also assumes salt formation in this reaction. His ideas may be formulated as follows:



These views have been criticized by Lachman.⁴⁵ He has shown that a small amount of the oxime salt of benzophenone is able to bring about the conversion of large amounts of the oxime into benzanilide. He has also observed that the rearrangement can be carried out in the presence of water. He concludes from his experiments that the rearrangement process consists in a direct conversion of the oxime salt into the anilide and free acid.



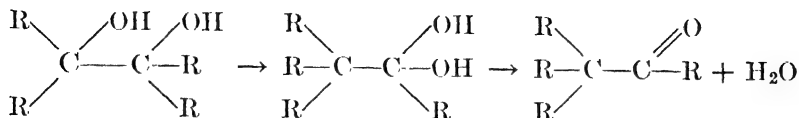
According to him, "dehydration of the oxime salt is an unnecessary preliminary step. Dehydrating agents merely help to furnish an anhydrous medium which is a prerequisite to the formation of oxime salts."

Lachman⁴⁶ has also criticized the fundamental idea of this concept of the intermediate formation of molecules with free valences in its application to other classes of molecular rearrangements. He is opposed to the interpretations of Tiffeneau and others, who picture rearrangements of the pinacol type as first involving a loss of water. He believes that the elimination of water is the last step in the reaction process, and that first there is a simultaneous exchange of an hydroxyl group and

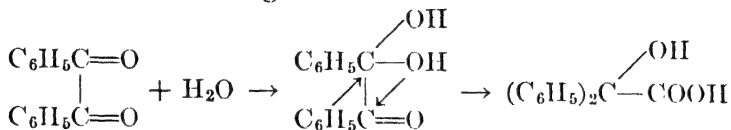
⁴⁵ Lachman, *J. Am. Chem. Soc.*, **46**, 1477 (1924); **47**, 260 (1925).

⁴⁶ Lachman, *ibid.*, **44**, 330 (1922); **45**, 1509 (1923). See, also, Kohler and Baltzly, *ibid.*, **54**, 4019 (1932).

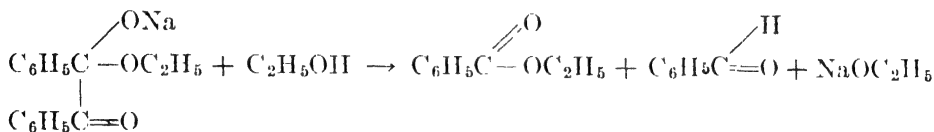
a radical. His mechanism involves the assumption of a mobile hydroxyl group, an idea first proposed by Lieben.⁴⁷



The same interpretation is used by him to explain the mechanism of the benzilic acid rearrangement.



The conversion of benzoin into diphenylacetic acid, and of dihydroxytartaric acid into hydroxymalonic acid, is pictured in a similar manner. As evidence for the necessity of the assumption of a mobile hydroxyl group Lachman cites the fact that the addition compound formed when one molecule of benzil is treated with one molecule of sodium ethylate does not rearrange in the absence of water, but decomposes in alcoholic solution into benzaldehyde and ethyl benzoate.



The addition compound contains no hydroxyl group. Only on the addition of water does rearrangement take place and produce benzilic acid. The significant observation of Kohler and Baltzly⁴⁸ is also of special interest from this point of view. These investigators have shown

that hexamethylbenzil, $(\text{CH}_3)_3\text{C}_6\text{H}_2\text{---C}(\text{O})\text{---C}(\text{O})\text{---C}_6\text{H}_2(\text{CH}_3)_3$, a compound in which hindrance prevents addition to the carbonyl group, does not undergo the benzilic acid rearrangement. This fact also gives character to the argument of those who believe that the first step in this rearrangement is an addition to the carbonyl group. Nef's⁴⁸ views are also shown to be untenable. Thus, Lachman has found that benzilic acid can be made to yield benzophenone and formic acid. Therefore the order is benzil \rightarrow benzilic acid \rightarrow benzophenone, and not as Nef postulated. His experimental results constitute a strong argument against the views of Michael,⁴⁹ who bases his mechanism on the preliminary addition of alkali. Lachman finds that the rearrangement takes place in water

⁴⁷ Lieben, *Monatsh.*, **23**, 63 (1902).

⁴⁸ Nef, *Ann.*, **298**, 372 (1897); **335**, 272 (1904).

⁴⁹ Michael, *J. Am. Chem. Soc.*, **42**, 812 (1920).

solution in the absence of alkali, although the rate of the reaction is slower. Neither does he accept the idea of Tiffeneau²⁰ that both carbonyl groups are involved. According to Lachman, addition of water takes place only on one ketone group. This appears to be supported by the fact that the addition compound which is formed with sodium alcoholate contains one molecule of benzil to one molecule of the ethylate. Scheuing⁵⁰ also supports this idea with experimental facts. This investigator has shown that in pyridine solution potassium hydroxide forms with benzil a compound of definite composition, $C_{14}H_{10}O_2 \cdot KOH$. At 0° this addition compound slowly rearranges to potassium benzilate; at 80° the conversion is rapid. According to Lachman's views this can

be expected since the addition compound,
$$C_6H_5-C \begin{array}{l} \nearrow OK \\ \downarrow \\ C_6H_5-C=O \end{array} \begin{array}{l} \nwarrow OH \\ \downarrow \end{array}$$
 contains an

hydroxyl group. Finally it should be pointed out that the experiments of Schönberg and Keller⁵¹ also indicate that the rearrangement does not involve both ketone groups. They have demonstrated that to bring about the reaction one molecule of reagent is necessary for every molecule of benzil. From all these facts Lachman has concluded that these changes are essentially oxidation-reduction processes, and as such involve a transfer of electrons. In the discussion of the electronic mechanism as a common basis for molecular rearrangements this mechanism will be considered again.

Other difficulties are encountered in the application of Tiffeneau's ideas to facts which have been discovered since the hypothesis was proposed. From the experiments of McKenzie and his co-workers,⁵² it has been shown that certain optically active pinacols and amino alcohols maintain an asymmetric configuration during rearrangement. It has also been shown that when certain optically active *tert.*-alkylcarbinols undergo the Wagner rearrangement optically active products are obtained.⁵³ On the basis of the intermediate formation of molecules with free valences these facts presuppose that such free radicals can possess a transient existence without loss of optical activity.

A survey of the chemical literature shows that certain recorded facts strongly indicate that this is not possible. Pickard and Kenyon⁵⁴ have

⁵⁰ Scheuing, *Ber.*, **56**, 252 (1923).

⁵¹ Schönberg and Keller, *Ber.*, **56**, 1638 (1923).

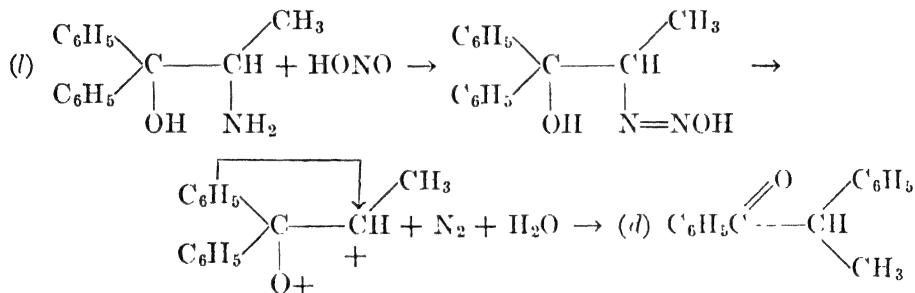
⁵² McKenzie and Richardson, *J. Chem. Soc.*, **123**, 79 (1923); McKenzie and Roger, *ibid.*, **125**, 841 (1924); McKenzie and Dennler, *ibid.*, **125**, 2105 (1924); McKenzie and Wills, *ibid.*, **127**, 283 (1925); see also *Ann. Repts. Chem. Soc. (London)*, **27**, 115 (1930); **30**, 184-185 (1933); McKenzie and Myles, *Ber.*, **65B**, 209 (1932); McKenzie, Roger, and Wills, *J. Chem. Soc.*, 779 (1926); McKenzie and Dennler, *Ber.*, **60B**, 220 (1927); McKenzie, Roger and McKay, *J. Chem. Soc.*, 2597 (1932).

⁵³ Wallis and Bowman, *J. Am. Chem. Soc.*, **56**, 491 (1934).

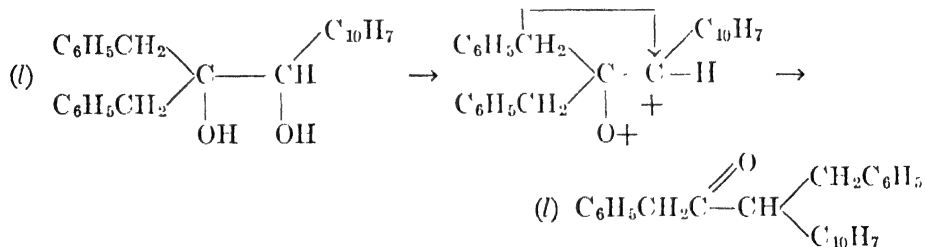
⁵⁴ Pickard and Kenyon, *J. Chem. Soc.*, **99**, 65 (1911).

shown that the action of magnesium on optically active alkyl halides gives optically inactive products. Other investigators have observed similar results. The spatial configuration of the valences in trivalent carbanions, free radicals, and carbonium ions has been studied by Wallis and Adams.⁵⁵ It is sufficient to mention only the fact that optically inactive products invariably resulted in all those metathetical reactions studied in which the intermediate formation of free radicals can justifiably be assumed to take place.

In order to explain the results obtained in their study of the optically active amino alcohols and glycols, McKenzie, Roger, and Wills⁵² adopted an ionic hypothesis similar in some respects to that suggested by Jones and Wallis^{32a} as a possible explanation of their results on the Curtius rearrangement. These investigators represent the action of nitrous acid on the optically active amino alcohols as follows:



The pinacols and glycols are formulated in a similar manner.



They assume that both electric charges are alike in the above scheme in order to account for the non-formation of stable ethylene oxides. This idea seems to be very unlikely, and it has been criticized by Haworth.⁵⁶ Haworth represents the charges as being of opposite sign and explains their neutralization by a migration of the phenyl group with its electron pair.

There are other objections to this hypothesis. In a study of certain spontaneous migrations of optically active groups from oxygen to sulfur

⁵⁵ Wallis and Adams, *J. Am. Chem. Soc.*, **55**, 3838 (1933).

⁵⁶ Haworth, *Ann. Repts. Chem. Soc. (London)*, **23**, 111 (1926).

Kenyon and Phillips⁵⁷ have shown that the rearrangement is accompanied by racemization. An investigation by Wallis and Adams⁵⁵ on the stability of the spatial arrangement of the groups in carbonium ions,

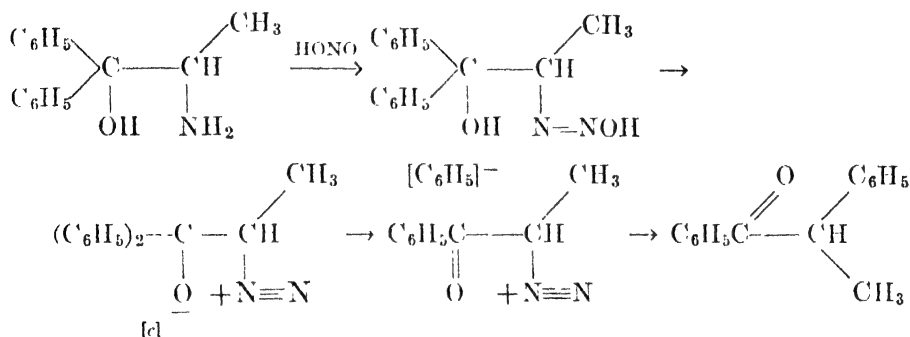
$\left[\begin{array}{c} R_1 \\ R_2 : \ddot{C} \\ R_3 \end{array} \right]^+$, has produced evidence which indicates that in the absence

of a special mechanism which leads to a Walden inversion such configurations are optically unstable. Only when the group is in the form

of the carbanion $\left[\begin{array}{c} R_1 \\ R_2 : \ddot{C} \\ R_3 \end{array} \right]^-$ does the spatial arrangement of the groups

in the ion appear to be sufficiently stable to maintain an asymmetric configuration.

In order to meet the objections to this concept in the form in which it has been applied by McKenzie and his co-workers, Kenyon, Lipscomb, and Phillips⁵⁸ proposed that the mechanism of the rearrangement be formulated as follows:



These investigators have pointed out that this interpretation has the advantage that it gives an explanation of the non-formation of the oxide "without departing from accepted theories of valency," and that it is not necessary to postulate that a positive charge plays the part of the fourth group, thereby assuming that carbonium ions can remain optically active in the free state.

Reflection will show that this mechanism also has its disadvantages. Its chief fault lies in the fact that in the rearrangement of the unstable complex, [c], the formation of a free negative ion, C_6H_5^- , is postulated. In the light of the experiments of Wallis and Moyer⁴¹ on the Hofmann rearrangement this can be considered to be a serious weakness. It is improbable that free negative phenyl ions are formed. Any idea of

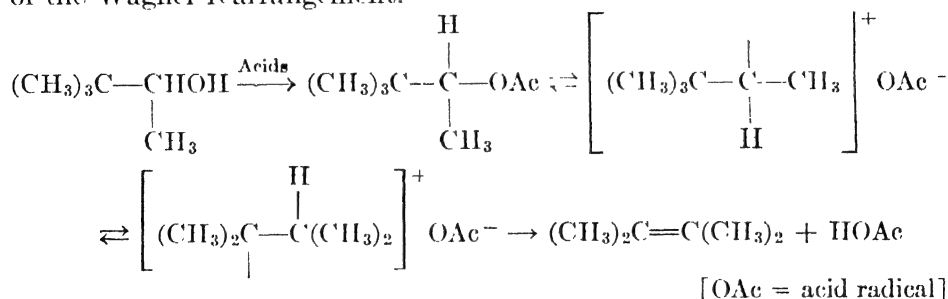
⁵⁷ Kenyon and Phillips, *J. Chem. Soc.*, 1676 (1930).

⁵⁸ Kenyon, Lipscomb, and Phillips, *ibid.*, 421 (1930).

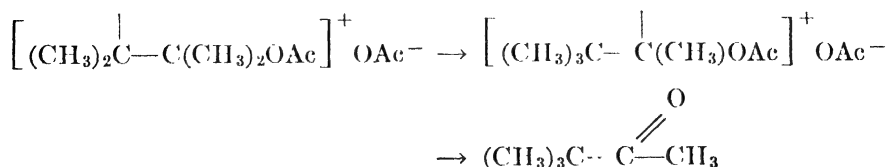
dissociation into ions of this type must take into account the energy requirements necessary to break the bonds. Here, also, as in the Curtius and Hofmann rearrangements the experimental evidence indicates that the reaction is unimolecular in its nature. Therefore, it would seem that ions are not involved, but a transference of electrons within the molecule itself, and that an electronic mechanism is to be preferred.

The ionic hypothesis has been advanced to explain the mechanism of other rearrangement processes. From the discussion of the application of the concept of the formation of intermediate cyclic compounds to the Wagner rearrangement it was seen that such an hypothesis tacitly assumes that changes of this type are brought about by the removal of water. However, it is known that there are instances in which water is not eliminated. It is also a fact that under suitable conditions (solvent, etc.) molecules of compounds which behave in this manner give evidence of ionization. This suggests an ionic hypothesis as an explanation of this type of rearrangement, and Meerwein and Wortmann⁵⁹ have formulated the change on this basis. According to them such an interpretation can also be used to explain those reactions in which water is lost during the rearrangement process. They believe that the cause of these changes is not to be found in the assumption of a loss of water as the first step of the rearrangement, but lies within the ion which is formed by electrolytic dissociation. The purpose of the acids which are used to bring about the rearrangement is to esterify the hydroxyl group. The esters so produced are assumed to be the ionizable molecules.

The formulation of the rearrangement of 3,3-dimethylbutanol-2 is given as an example of the application of their ideas to the mechanism of the Wagner rearrangement.



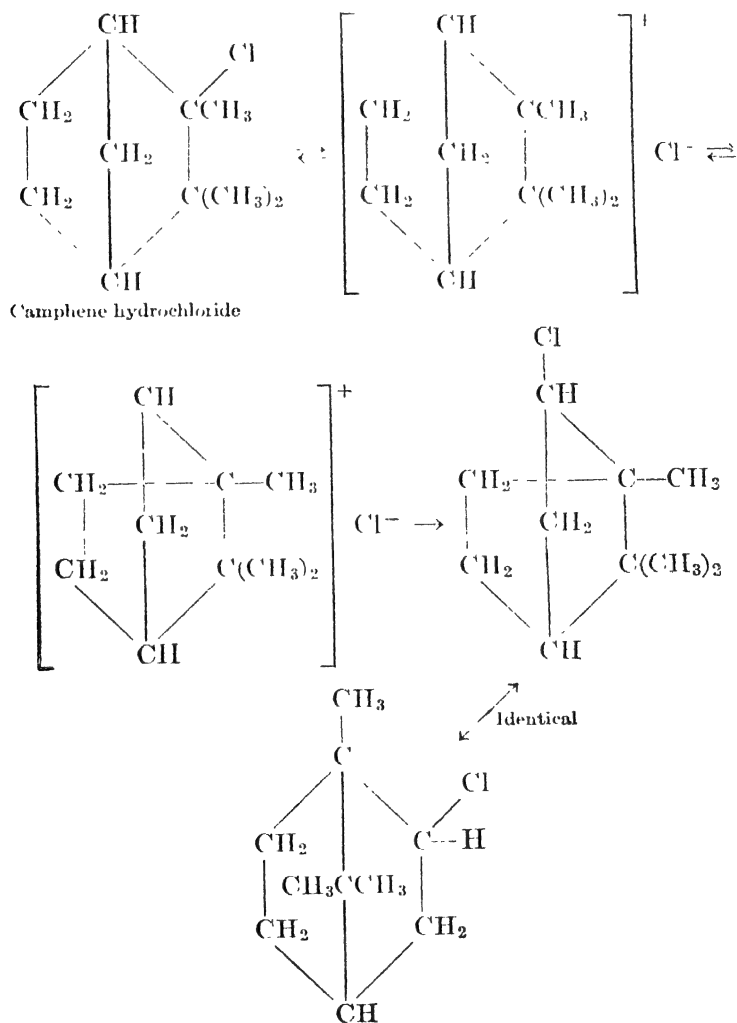
The pinacol rearrangement is explained in a similar manner.



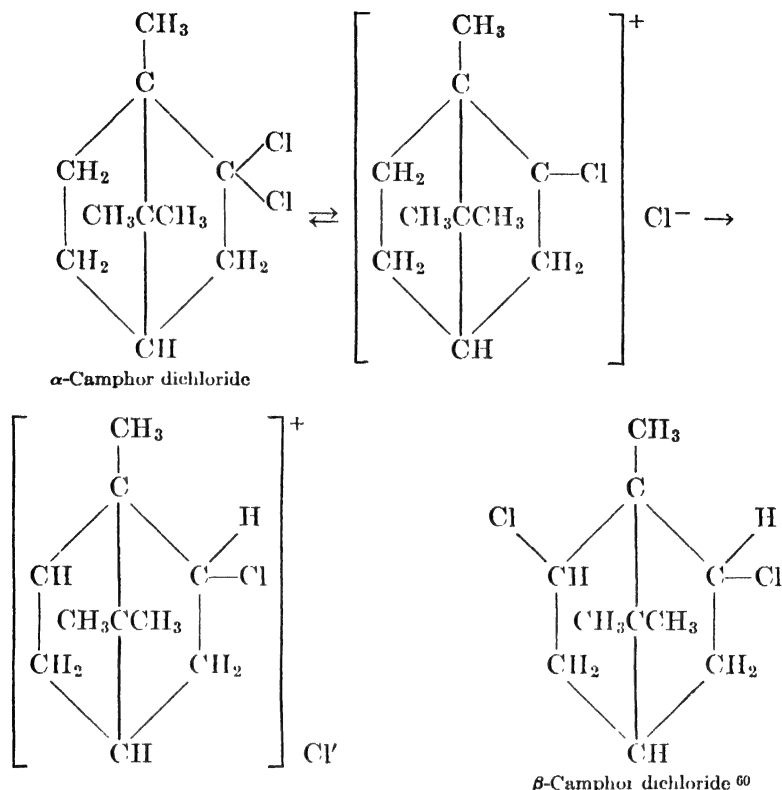
⁵⁹ Meerwein and Wortmann, *Ann.*, **435**, 190 (1924).

The fact that the reverse change does not occur is explained on the basis of the instability of the pinacolone esters.

They explain the behavior of certain halogen compounds of the camphor series on the basis of this hypothesis. In the presence of dissociating solvents (cold alcoholic hydrochloric acid, etc.), camphene hydrochloride rearranges to give isobornyl chloride. It is known that these compounds have properties which are in many respects similar to the triarylmethyl halides. For instance, they yield ethers on treatment with alcohols. When shaken with water, camphene hydrochloride gives camphene hydrate. These facts strongly suggest that in solution the hydrochloride is ionized. The change of this compound into isobornyl chloride is represented by Meerwein and Wortmann as follows:⁵⁹



A similar mechanism is used to explain the conversion of α -camphor dichloride into β -camphor dichloride.



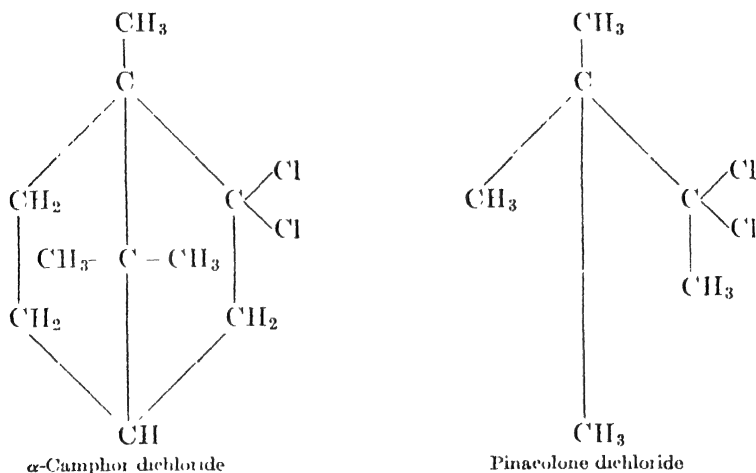
This rearrangement takes place easily under conditions similar to those used in the conversion of camphene hydrochloride into isobornyl chloride. It is significant that in phenol solution the change is rapid, but that it is slow in solvents of low dielectric constant unless stannic chloride is present. A very slow change takes place in ligroin solution. It is more rapid in benzene, and still more rapid in ionizing solvents such as nitrobenzene.

The relationships which exist between fenchyl alcohol, isofenchyl alcohol, α -fenchene hydrate, and β -fenchene hydrate are also explained on the basis of this hypothesis. Other rearrangements in the camphor series are discussed.

From what has been written it can be seen that Meerwein and Wortmann give an interpretation to these rearrangements in the camphor

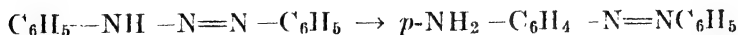
⁶⁰ Meerwein and Wortmann formulated β -camphor dichloride as 2,6-dichlorocamphane. The experiments of Lipp and Lausburg [*Ann.*, **436**, 274 (1924)] indicate that it is 2,10-dichlorocamphane.

series which is similar to their explanation of the dehydration of *tert.*-alkylcarbinols. On the basis of their proposed mechanism these halides are considered to be esters of hydrochloric acid. In discussing the relationships which exist between α - and β -camphor dichlorides they point out that these halides bear a relationship to each other similar to that which formally exists between the dichlorides of pinacol and pinacolone. They show this analogy in the following manner:



However, in studying the properties of pinacolone dichloride they found that this substance cannot be converted into the corresponding dichloride of pinacol. Neither can the change be brought about in the reverse direction. This fact is significant since in these compounds the tendency to ionize is not present. As Ingold⁶¹ has pointed out, it is "an indication that special structural conditions are necessary for rearrangement by the ionic mechanism." It also strongly suggests that such a concept should not be unrestricted in its application but should be used only when it is known beforehand by some other method that ions are present.

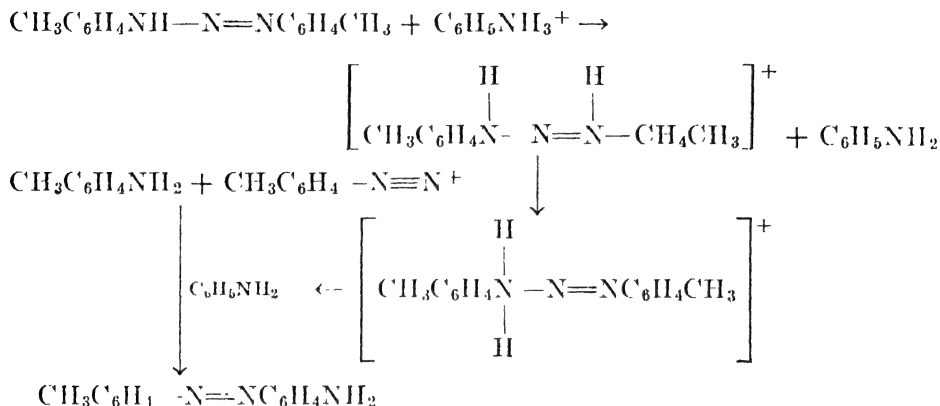
It is now our purpose to consider a few such cases. The diazoamino rearrangement will serve as our first example.



It is to be recalled that this rearrangement is best carried out in aniline in the presence of aniline hydrochloride; that is, it is catalyzed by the anilinium ion. It is also to be noted that the reaction is not intramolecular. Experimental evidence shows that the process involves pre-dissociation followed by a recombination. The results of Rosenhaver

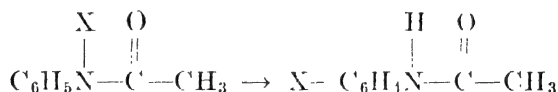
⁶¹ Ingold, *Ann. Repts. Chem. Soc. (London)*, **21**, 99 (1924).

and Unger⁶² and of Kidd⁶³ bear out this statement, for the rearrangement of $\text{CH}_3\text{—C}_6\text{H}_4\text{—NH—N=N—C}_6\text{H}_4\text{CH}_3$ in the presence of aniline and of its hydrochloride yields as the main product, not the compound expected, but $\text{NH}_2\text{C}_6\text{H}_4\text{—N=NC}_6\text{H}_4\text{CH}_3$ instead. The following mechanism has, therefore, been proposed:



This mechanism also suggests the reason for the low yield when the reaction is carried out in the presence of water. The rate of formation of the phenol from the diazonium ion comes into consideration, and since this rate is comparable to that of the rate of coupling the yield of the desired product is greatly diminished.

Ions are also probably involved in the rearrangement of N-haloacetyl-anilides

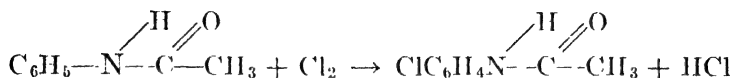
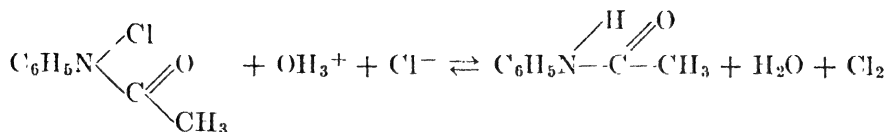


for it is known that in the case of N-chloroacetyl-anilides the reaction is catalyzed in aqueous solutions by hydrochloric acid. There is also evidence which shows that in such solutions the speed of the reaction depends on the activity of the hydrochloric acid present. Further interesting facts have been reported by Olson and his co-workers.⁶⁴ These investigators have studied the reaction in the presence of radioactive chloride ions, and they report that the radioactive halogen enters into the molecule faster than the rate of rearrangement takes place. To some this has suggested the following formulation.

⁶² Rosenhaver and Unger, *Ber.*, **61**, 392 (1928).

⁶³ Kidd, *J. Org. Chem.*, **2**, 198 (1937).

⁶⁴ Olson, Halford, and Hornel, *J. Am. Chem. Soc.*, **59**, 1613 (1937) Olson and Hornel *J. Org. Chem.*, **3**, 76 (1938): see this article for other references.



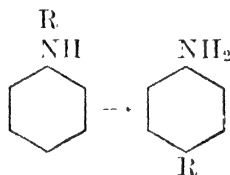
This is hardly the complete picture for the process, nowever, since in all reactions of this type the yields are never good and many by-products are produced. Finally, it may be added that in the case of the corresponding N-bromoacetanilide bromine cannot be an intermediate because Bell⁶⁵ has shown that the rate of reaction of bromine on acetanilide is such as not to allow this formulation.

Neither can mechanisms of this type be used to explain the benzidine rearrangement.



Although the reaction is catalyzed by acids there is good evidence that in such cases the rearrangement is intramolecular and that dissociation into ions does not take place. This evidence will be given later when the electronic concept is discussed.

The rearrangement of N-alkylanilinium salts to alkyanilines may now be considered



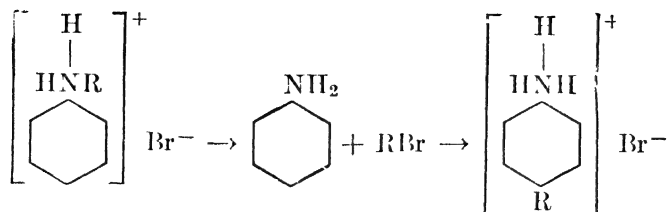
This rearrangement which was first discussed by Hofmann has been very extensively studied and many theories concerning its mechanism have been advanced.⁶⁶ At this time, however, only two points of view need to be considered.

Michael⁶⁷ has stated that the most plausible course of this reaction is a dissociation of the salts into aniline and the alkyl halide. The halide then reacts with the hydrogen atom of the aromatic nucleus.

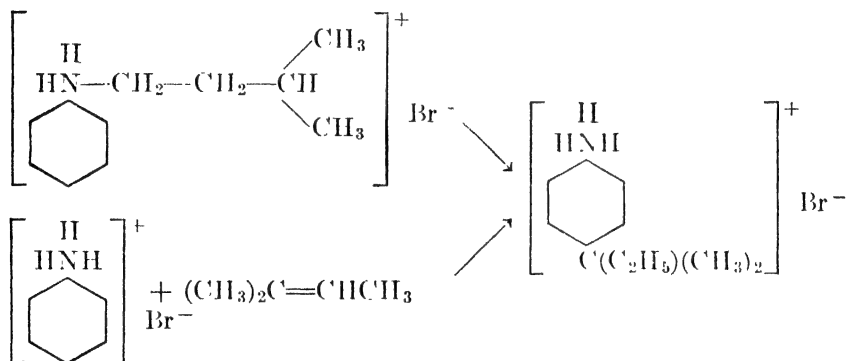
⁶⁵ Bell, *J. Chem. Soc.*, 1151 (1936).

⁶⁶ Benz, *Ber.*, **15**, 1646 (1882); Nolting and Baumann, *Ber.*, **18**, 1150 (1885); Nolting and Forel, *Ber.*, **18**, 2681 (1885); Limpach, *Ber.*, **21**, 640 (1888); Hodgkin and Limpach, *J. Chem. Soc.*, **61**, 420 (1892); Reilly and Hickinbottom, *ibid.*, **117**, 103 (1920).

⁶⁷ Michael, *J. Am. Chem. Soc.*, **42**, 787 (1920).



Hickinbottom and co-workers⁶⁸ have tested this theory experimentally and have concluded that dissociation does not take place in this manner. In a study of the rearrangement of isoamylaniline hydrobromide⁶⁸ they have shown that, on heating, an isomerization of the group takes place, and that *p*-amino-*tert*-amylbenzene is obtained. Some trimethylethylene is also formed. They also investigated the action of this hydrocarbon on aniline hydrobromide, finding that, "under conditions strictly comparable with those required for the rearrangement of isoamylaniline hydrobromide," the product was *p*-amino *tert*-amylbenzene.



Thus, they have concluded that the formation of the nuclear substituted aniline is due to the intermediate formation of trimethylethylene since each phase of this mechanism has been realized experimentally. This conclusion may be questioned.

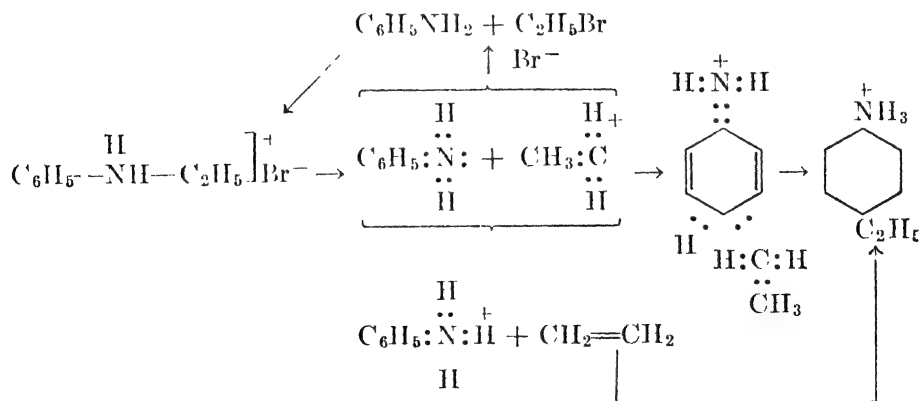
Difficulties are encountered in explaining certain other results obtained by Hickinbottom.⁶⁸ If the above reaction is carried out in the presence of certain metallic halides *p*-aminoisoamylbenzene is produced. Here the formation of an intermediate trimethylethylene cannot be used to explain the results, for this olefin reacts with aniline either in the presence or absence of metallic halides to give the isomeric *tert*-amyl compound. A similar fact is also observed with isobutylaniline.⁶⁴ The product of rearrangement in the presence of hydrogen chloride or bro-

⁶⁸ Hickinbottom, *J. Chem. Soc.*, 64, (1927); Hickinbottom and Waine, *ibid.*, 1558 (1930); Hickinbottom and Preston, *ibid.*, 1566 (1930); Hickinbottom, *ibid.*, 2396 (1932); 946, 1070 (1933); 319 (1934); *Nature*, **131**, 762 (1933).

mide is quite distinct from that which is formed when the rearrangement of the free amine is brought about by dry metallic salts. In the former case *p*-amino-*tert*.-butylbenzene is formed; *p*-aminoisobutylbenzene is produced in the latter reaction. Therefore, either this mechanism must be abandoned, or else it must be assumed with Hickinbottom that the reaction in the presence of metallic salts follows a different course.

There are doubts about the latter view, and it has been criticized by Bennett and Chapman.⁶⁹ These writers believe that a simpler explanation lies in Michael's⁶⁷ interpretation of such rearrangements, and that both types of products are formed from the same intermediate compounds. When heated alone the hydrobromide is assumed to dissociate rapidly to produce a large proportion of alkyl bromide which isomerizes in the vapor phase to the *tert*.-bromide. This compound then combines with aniline. When the reaction is carried out in the presence of metallic halides the rate of formation of the alkyl bromide is so much slower that substitution in the nucleus occurs before isomerization. It should be noted, however, that this explanation has its weakness in that as yet it lacks experimental verification. In fact, experiments by Hickinbottom and Waime⁶⁸ indicate that it is impossible to reconcile it with the facts.

More recently Hickinbottom⁷⁰ has taken the position that the most probable course of the reaction is through an intermediate which postulates the formation of a carbonium ion of the migrating alkyl group. On this hypothesis the behavior of ethylaniline hydrobromide is represented by the following scheme:

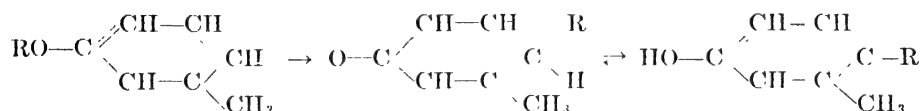


The rearrangement of alkyl phenyl ethers is of especial interest from this point of view. Since this reaction is catalyzed by acids it is again

⁶⁹ Bennett and Chapman, *Ann. Repts. Chem. Soc. (London)*, **27**, 124 (1930).

⁷⁰ Hickinbottom, *J. Chem. Soc.*, 1700 (1934).

tempting to assume a mechanism involving the carbonium ion of the migrating alkyl group as the intermediate. Indeed we can find evidence in the literature which gives credence to this belief. Short and Stewart⁷¹ have found evidence which shows that this rearrangement is not intramolecular, at least in some cases, for when ethyl phenyl ether rearranges in anisole as a solvent *p*-ethylanisole is formed. When a longer alkyl group is used rearrangements within the group itself occur. These are typical reactions of a carbonium ion. Sowa, Hinton, and Nieuwland⁷² also have submitted facts which are best explained on the assumption that the change involves at least two molecules of the ether. Niederl and Natelson,⁷³ however, are opposed to the idea that such rearrangements are intermolecular. They also reject for the most part the views of Van Alphen,⁷³ Claisen,⁷⁴ and Hurd and Cohen.⁷⁵ According to them the most plausible explanation is a reaction mechanism which is unimolecular in its nature, and which is based upon the considerations of Lapworth⁷⁶ and of Latimer.⁷⁷ It should be pointed out that valid



objections can be raised against Niederl's proposed mechanism. For example, the interpretation gives one no explanation of the presence of unsaturated hydrocarbons and of unsubstituted cresols or other phenols which are generally formed in rearrangements of this type. Neither does it account for the fact that often in rearrangements of alkyl phenyl ethers the alkyl radical isomerizes to another group during the reaction process. It cannot be used to explain the experimental results obtained by Cox⁷⁸ in his investigations of the closely allied Fries "rearrangement" of phenolic esters. Here it is quite certain that when these esters are acted upon by such reagents as aluminum chloride or zinc chloride a scission of the molecule takes place, and acid chlorides are formed as intermediates which then react with the phenol to pro-

⁷¹ Short and Stewart, *J. Chem. Soc.*, 553 (1929).

⁷² Sowa, Hinton, and Nieuwland, *J. Am. Chem. Soc.*, **54**, 2019, 3694 (1932); **55**, 3402 (1933).

⁷³ Van Alphen, *Rec. trav. chim.*, **46**, 799 (1927); Niederl and Natelson, *J. Am. Chem. Soc.*, **54**, 1063 (1932); Niederl and Storeh, *ibid.*, **55**, 284 (1933); Smith, *ibid.*, **55**, 849 (1933).

⁷⁴ Claisen and Eisleb, *Ann.*, **401**, 21 (1913); Claisen, *ibid.*, **418**, 69 (1919); Claisen and Tietze, *Ber.*, **58**, 275 (1925); **59**, 2344 (1926).

⁷⁵ Hurd and Cohen, *J. Am. Chem. Soc.*, **53**, 1917 (1931).

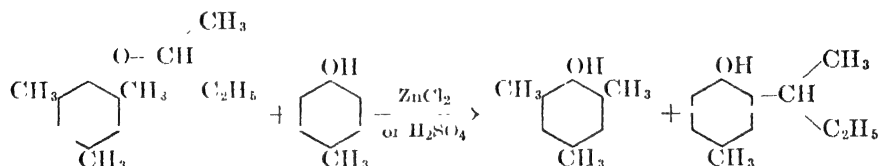
⁷⁶ Lapworth, *J. Chem. Soc.*, **73**, 445 (1898).

⁷⁷ Latimer, *J. Am. Chem. Soc.*, **51**, 3185 (1929).

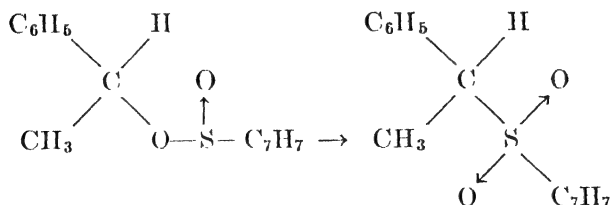
⁷⁸ Fries and co-workers, *Ber.*, **41**, 4276 (1908); **43**, 214 (1910); **54**, 717 (1921); **56**, 1305 (1923); Auwers, *Ann.*, **421**, 36 (1920); Cox, *J. Am. Chem. Soc.*, **52**, 352 (1930); Skraup and Poller, *Ber.*, **57**, 2033 (1924); Skraup and co-workers, *Ber.*, **60**, 942, 1070 (1927).

duce ketones, for, in the presence of an inert solvent, such as diphenyl ether, acyl derivatives of diphenyl ether are formed. Thus, the evidence supports the hypothesis of Skraup and Poller ⁷⁸ and indicates that the reaction process is not in reality a true rearrangement but is intermolecular in its nature.

In this connection some experimental results of Wallis and his co-workers ⁷⁹ are of interest. They have studied the nature of the products formed in the Claisen rearrangement of certain optically active ethers. Although with *d*- and *l*-*sec*-butyl *m*-cresyl and *d*- and *l*-*sec*-butyl *p*-cresyl ethers they found that the substituted phenols obtained by rearrangement were optically active, they did observe that the rearrangement was accompanied by partial racemization. Furthermore, when experiments were devised to determine whether an alkyl radical containing an asymmetric carbon atom is actually able as a carbonium ion to enter a foreign nucleus without resultant loss of optical activity, the results obtained showed that this was not possible. In their experiments on the point in question they prepared *d*- and *l*-*sec*-butyl mesityl ethers and studied the nature of the products formed when the reaction was carried out in the presence of *p*-cresol.



The 4-methyl-2-*sec*-butylphenol, however, in both cases, was completely inactive. It can be definitely concluded, therefore, that an intermolecular carbonium-ion mechanism cannot be used to explain the retention of optical activity in the experiments on *d*- and *l*-*sec*-butyl *m*-cresyl and *p*-cresyl ethers. At least part of the rearrangement products are formed by an intramolecular process in which no carbonium ions occur. In this latter case an electronic mechanism is the more probable. A similar result has been reported in studies ⁸⁰ on the rearrangement of sulfinic esters.

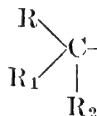


⁷⁹ Sprung and Wallis, *J. Am. Chem. Soc.*, **56**, 1715 (1924); Gilbert and Wallis, *J. Org. Chem.*, **5**, 184 (1940).

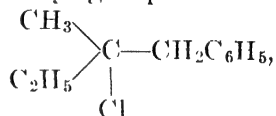
⁸⁰ Kenyon and Phillips, *J. Chem. Soc.*, 1676 (1930); Argus, Balfe, and Kenyon, *ibid.*, 485 (1938).

The optically active sulfinate yields largely the completely racemized sulfone. In the small amount of the optically active sulfone so produced the configuration on the asymmetric carbon atom seems to be maintained. If this rearrangement involved carbonium ions this would not have been expected. Here again at least part of the product formed is produced by an intramolecular electronic change. Such changes will be more fully discussed later.

The ionic concept is also of interest when applied to explain the mechanism of the Wagner rearrangement which takes place when certain reactions are carried out on *tert.*-alkylecarbinols. Wallis and Bowman⁸¹ have studied the nature of the products formed when the hydroxyl group in an optically active alcohol of the type



stituted by chlorine. It has been found that, when the compound 2-methyl-2-phenylbutanol-1 is treated with thionyl chloride, the rearrangement takes place with a migration of the phenyl group. A tertiary chloride 2-chloro-2-methyl-1-phenylbutane,

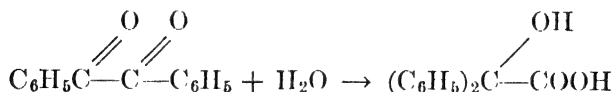


and an unsaturated hydrocarbon, 2-methyl-1-phenylbutene-1,

$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{C} = \text{CHC}_6\text{H}_5 \\ \diagdown \\ \text{C}_2\text{H}_5 \end{array}$, are formed. It has also been observed that the

tertiary chloride as formed, though largely racemic, possesses some optical activity. Since it is known that the first product of the reaction of an alcohol and thionyl chloride is a compound of the type, $\text{R} - \text{OS}(=\text{O})\text{Cl}$, it is probable that the portion of the chloride which has maintained an asymmetric configuration again has been formed through a rearrangement which is internal and consequently electronic in its nature.

Ionic hypotheses have been used to explain other types of rearrangements. The rearrangement of benzil to benzilic acid may be considered.

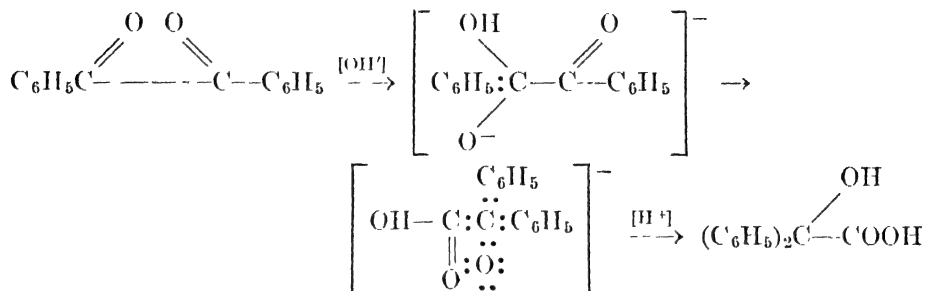


Recent work by Westheimer⁸² on this change shows that this reaction is catalyzed by hydroxide ion with no measurable catalysis by other basic ions such as the phenolate ion or *o*-chlorophenolate ion

⁸¹ Wallis and Bowman, *J. Am. Chem. Soc.*, **56**, 491 (1934)

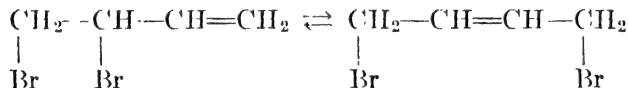
⁸² Westheimer, *ibid.*, **58**, 2209 (1936).

Furthermore, Roberts and Urey ⁸³ in their studies on oxygen exchange report that the rearrangement is slower than the oxygen exchange which is likewise catalyzed by bases. To explain these results the reaction has been formulated by a shift of a phenyl group with its electron pair with subsequent addition of a proton to yield benzoic acid.

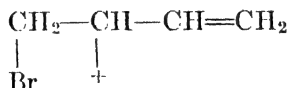


We shall see later, however, that the migration of the phenyl group with its electron pair does not take place as a negative ion. The shift of the group takes place in such a manner that again we should view the rearrangement as being that of an electronic change.

The rearrangement of the butadiene dibromides is of interest from the viewpoint of an ionic mechanism.



The rearrangement takes place rapidly at 100°, and it constitutes one of the main controversial points in the settlement of the question of addition of halogens to conjugated systems of double bonds (p. 669). According to Ingold ^{61, 84} this change can be explained best on the basis of an ionic mechanism. He assumes that during the initial addition process ions are formed, and that "since the second bromine atom is liberated (as anion) only during the addition of the first, the initial product of addition . . . consists of the ions of the 1,2-dibromide."



What happens after this initial stage of the reaction process depends on the conditions of the experiment. In a non-ionizing medium association takes place and a 1,2-addition compound is formed. Under these conditions the production of any 1,4-addition product results from a re-

⁸³ Roberts and Urey, *ibid.*, **60**, 880 (1938).

⁸⁴ Ingold, *Ann. Repts. Chem. Soc. (London)*, **25**, 124-134 (1928); Burton and Ingold, *J. Chem. Soc.*, 904 (1928); Ingold and Shoppee, *ibid.*, 1199 (1929); Ingold and Smith *ibid.*, 2752 (1931); Burton and Ingold, *ibid.*, 2022 (1929).

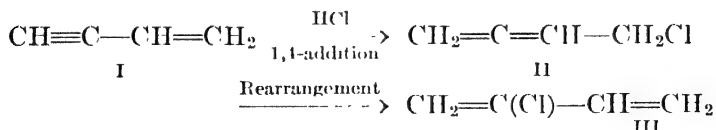
arrangement of the 1,2-dibromide. In this respect Ingold's ideas are in agreement with the suggestions of Gillet,⁸⁵ who believes that 1,4-addition is in reality preceded by 1,2-addition and rearrangement. Ingold believes that in an ionizing medium a distribution of the charge takes place and therefore "in a general case a mixture of bromides results, the composition of which will depend on the attached groups."

In support of these ideas Ingold and Smith⁸⁴ point out that iodine chloride adds to butadiene to give a mixture of



They argue that this indicates "an initial entrance of iodine at the α -carbon atom," and therefore conforms with the ideas outlined in the preceding paragraph. It is of interest to note, however, that the experimental results of Muskat and Northrup⁸⁶ on the chlorination of butadiene cannot be explained so easily. They carried out the chlorination in non-ionizing solvents, and in each case considerable amounts of the 1,4-dichloride were formed. They also observed that these two chlorides do not rearrange into one another, as do the dibromides. These facts make it evident that the formation of 1,4-butadiene dichloride in a non-ionizing solvent cannot be explained by the interpretation advanced by Ingold. They seem, on the other hand, to confirm the ideas of those who believe that in halogen addition to butadiene there is a simultaneous formation of 1,2- and 1,4-dihalides, and that the relative proportions of the two compounds formed in any one experiment depend upon the conditions (temperature, solvent, presence or absence of peroxides, etc.).⁸⁷

The addition of hydrogen chloride to vinylacetylene is also of interest from this point of view. Carothers and Berchet⁸⁸ have shown that the first product of the reaction is 4-chlorobutadiene-1,2. This compound is sufficiently stable to be converted into its carbinol. However, in the presence of cuprous chloride and hydrochloric acid it readily rearranges into 2-chlorobutadiene-1,3. Their experiments show that the reactions take place in the following order.



The reaction product of phenylmagnesium bromide on (II) reacts with water to give a derivative of (III), 2-phenylbutadiene-1,3. The iso-

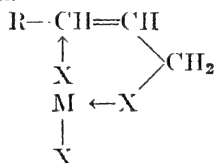
⁸⁵ Gillet, *Bull. soc. chim. Belg.*, **31**, 366 (1922).

⁸⁶ Muskat and Northrup, *J. Am. Chem. Soc.*, **52**, 4043 (1930).

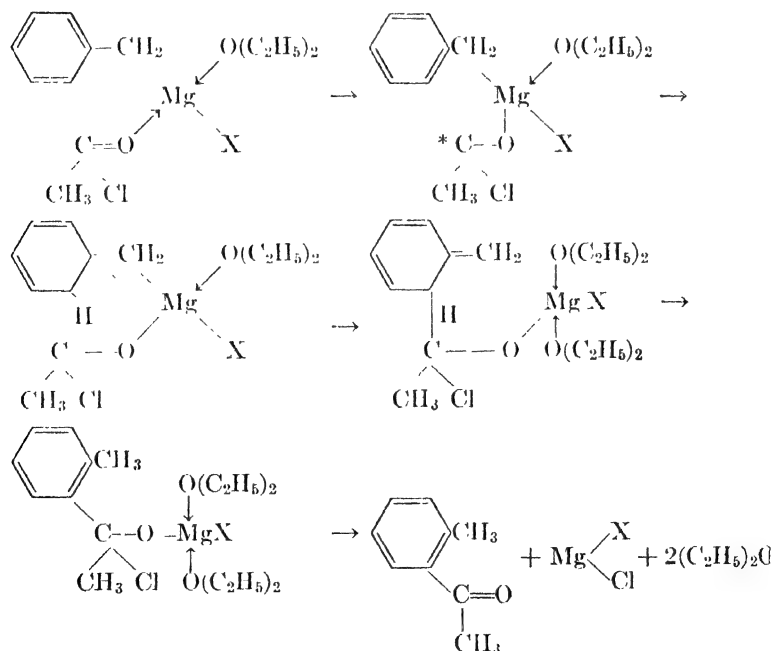
⁸⁷ Kharasch and co-workers, *ibid.*, **55**, 2468, 2521, 2531 (1933); **56**, 244, 712, 1212, 1243, 1642, 1782 (1934); **57**, 2463 (1935); **58**, 57 (1936); *J. Org. Chem.*, **1**, 393 (1936).

⁸⁸ Carothers and Berchet, *J. Am. Chem. Soc.*, **55**, 2807 (1933).

meric chloride (III) does not react with the Grignard reagent. These investigators believe that these and other results which they have reported show that α,γ -rearrangements of this type cannot proceed by any mechanism involving free ions. The reactions are intramolecular in their nature. They prefer to consider these changes as being brought about by a mechanism which assumes the formation of an additive complex. Chelation and opening of the ring result in the abnormal products which they obtain.



Johnson⁸⁹ explains the abnormal reactions of benzylmagnesium chloride on the basis of a similar mechanism. For example, acetyl chloride reacts with benzylmagnesium chloride to give *o*-tolyl methyl ketone. Almost none of the "normal" product, benzyl methyl ketone, is produced. This fact is explained on the assumption that an additive complex of the following type is formed. A shift of electrons then takes place followed by an "intramolecular chelation." Opening of this chelate ring produces the rearrangement product.



* The carbon marked by an asterisk has a sextet of electrons.

⁸⁹ Johnson, *ibid.*, **55**, 3029 (1933); Austin and Johnson, *ibid.*, **54**, 647 (1932).

Other examples are known and could be discussed, such as the allylic rearrangements which have been studied by Prévost, but the illustrations which have been given are sufficient to show the applicability of this concept to rearrangement processes. Often it appears that these changes which at first might seem explicable on the basis of predissociation are in reality purely intramolecular in their nature, and that the electronic displacements and shifts which produce these reactions take place within the molecule itself. In such rearrangements an electronic mechanism is to be preferred.

THE ELECTRONIC CONCEPT AS AN EXPLANATION OF INTRAMOLECULAR REARRANGEMENTS

In the preceding sections of this chapter those interpretations have been discussed which in one form or another have explained rearrangement processes on the basis of predissociation either into radicals or ions. It has been shown in many instances that the application of this concept is very limited and that for many rearrangements the explanations are wholly inadequate. The failure of these interpretations as explanations of the mechanism of molecular rearrangements is due to the fact that those investigators who proposed them did not realize that such reactions often are dependent on properties inherent in the molecules themselves, and for that reason cannot take place in a step-by-step fashion, but must be continuous processes which involve simple displacements or transference of electrons from one atom to another within the molecule.

In a brilliant paper entitled "Applications of the Electronic Conception of Valence," Jones⁹⁰ first examined intramolecular rearrangements from this point of view. In a discussion of reactions which are known to take place among certain classes of compounds containing nitrogen his considerations led him to put forward the fundamental generalization that "a carbon atom when linked directly to a nitrogen atom does not readily take from it negative electrons, or in other words is not readily reduced by it," but rather "the tendency of the system is to pass to one in which the carbon atom is as fully oxidized as possible and the nitrogen atom as fully reduced as possible." The relationships which exist between the amines, aldimides, nitriles, nitrile oxides, isonitroparaffins, and hydroxamic acids, and also the aldoximes, amides, isocyanates, and the carbamic acids are explained on this basis. In applying this principle to intramolecular rearrangements of the Curtius, Hofmann, Lossen, and Beckmann types, Jones arrived at the con-

⁹⁰ Jones, *Am. Chem. J.*, **50**, 414 (1913).

clusion that these rearrangements are not essentially different in mechanism. In the conclusion of his argument he states, "In my opinion . . . [these rearrangements] all have in common, intramolecular oxidation and reduction, or an exchange of negative electrons between the carbon atom and the nitrogen atom. In fact if all of the reactions classed as examples of the Beckmann rearrangement (including the Hofmann and Curtius reactions) are inspected it will be observed *that in every case the rearrangement is accompanied by a process of intramolecular oxidation and reduction*. It seems very probable that this tendency . . . may be the real determining factor in the Beckmann rearrangement, and that the formation of univalent nitrogen, proposed by Stieglitz as the immediate cause, may be a mere incident, necessary, to be sure, to pave the way for the change. . . . Stieglitz claims that the rearrangement is induced by the potency of the free valences of univalent nitrogen. The present mode of viewing the rearrangement would speak rather of the potency of the carbon atom to lose negative electrons, and of the nitrogen atom to acquire them, and would look upon the free valences of univalent nitrogen as the stage-setting required to furnish a suitable environment in which the essential action may take place."

Essentially the same ideas have been expressed independently by Stieglitz.⁹¹ Robinson⁸⁵ and Ingold⁹¹ also have believed for a long time that intramolecular rearrangements involve a transference of electrons within the molecule and consequently are best explained on the basis of an electronic mechanism.

With these ideas in mind Whitmore⁹² has proposed that a more general application of this concept should be made, and that the mechanism of the migration of groups in all intramolecular rearrangements be placed on a common basis and be explained on the supposition of a transference of electrons within the molecule. According to him the structures of organic molecules which undergo intramolecular rearrangements can be represented electronically by one of the following general formulas:



in which X is a strongly electronegative atom, and A, B, and D are atoms which are neither strongly electronegative nor electropositive. System 1 contains those molecules which undergo rearrangements of the Beckmann, Curtius, Hofmann, and Lossen types. Other rearrangements such as the pinacol and allied rearrangements are also included

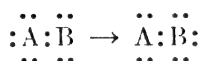
⁹¹ *Ann. Repts. Chem. Soc. (London)*, **20** (1923); **21** (1924).

⁹² Whitmore, *J. Am. Chem. Soc.*, **54**, 3274 (1932).

in this system. The allylic rearrangements take place in molecules which belong to system 2.

When molecules of either of these two types enter into chemical reaction in such a manner as to remove the atom X from the system it is postulated by Whitmore that X takes with it its shared pair of electrons and leaves the atom B or D, as the case may be, with an incomplete shell of six electrons. The course of the reaction from this point is determined by the changes which take place in the fragment $\begin{smallmatrix} \ddot{A} & \ddot{B} \\ | & | \\ \ddot{\cdot} & \ddot{\cdot} \end{smallmatrix}$.

Under suitable conditions it may take up a negative ion $\begin{smallmatrix} \ddot{Y} \\ | \\ \ddot{\cdot} \end{smallmatrix}$ from the reaction mixture. This yields the normal product $\begin{smallmatrix} \ddot{A} & \ddot{B} & \ddot{Y} \\ | & | & | \\ \ddot{\cdot} & \ddot{\cdot} & \ddot{\cdot} \end{smallmatrix}$. Another possibility must be considered if one of the groups attached to A is a hydrogen atom. The fragment can now also lose a proton. Under these conditions olefinic compounds are produced. Thus, it is seen that on the basis of this mechanism olefins are not necessarily intermediate products in a chemical reaction but are formed as products of "side" reactions. This interpretation is significant, for it explains why the concept of the intermediate formation of olefinic compounds, which has been discussed previously, fails as an explanation of molecular rearrangement processes. The third possibility, perhaps the most important, is stated by Whitmore as follows: "The nature and environment of A and B may be such that B has the greater attractions for electrons or that A can more readily dispense with a pair of its electrons. In either case a change in the fragment will leave A with an open sextet.



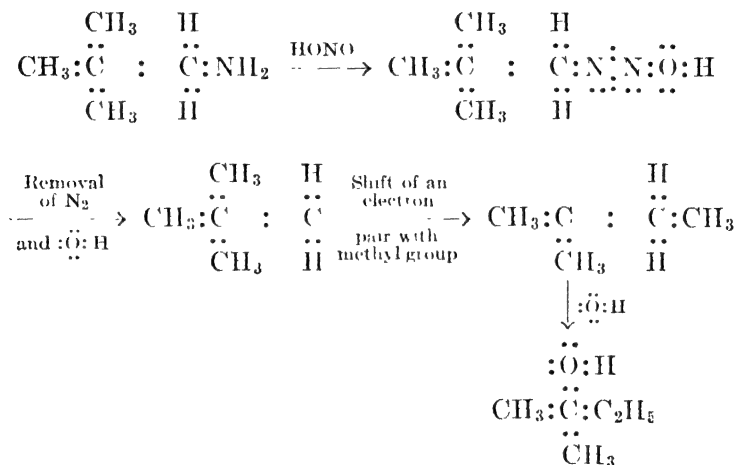
The shift of the electron pair includes the atom or group which it holds. The new fragment can then recombine with the ion X or with a new negative ion Y from the reaction mixture. The result is an 'abnormal' or 'rearranged product.' In this manner either the compound XAB or YAB is formed."

Whitmore also has discussed the nature of the products which may be formed when one of the groups attached to the rearranged fragment is a hydrogen atom. Here again as in the original fragment the system can stabilize itself by the loss of a proton. However, it can be readily seen that the unsaturated compound so formed may not be the same as that obtained in the former case.

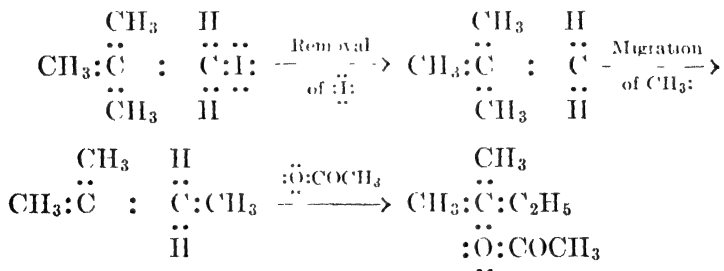
This reaction mechanism can be successfully applied to many types of intramolecular rearrangements. It has also been very useful as an aid in the determination of the nature of "abnormal" products which

are often formed in chemical reactions, and in foreseeing when rearrangements are to be expected. The following examples are given for the purpose of showing its range of application.

It is well known that the action of nitrous acid on amines often produces compounds which are products of a molecular rearrangement. Thus, when neopentylamine is treated with nitrous acid dimethylethylcarbinol is obtained. None of the corresponding *tert*.-butylcarbinol is formed in the reaction. On the basis of the mechanism under discussion the reaction is formulated as follows:



Other reactions of *tert*.-butylcarbinol and its derivatives can be explained in a similar manner. For example, the preparation of *tert*.-amyl acetate from neopentyl iodide is explained by Whitmore as follows:

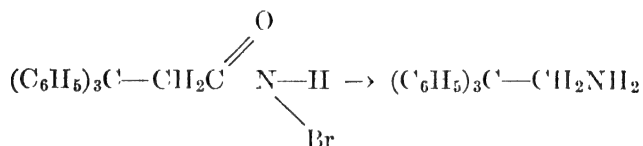


The preparation of *tert*.-butyl compounds from isobutyl alcohol and its derivatives is easily explained on the basis of this mechanism. This concept also accounts for the failure of all attempts to prepare halides

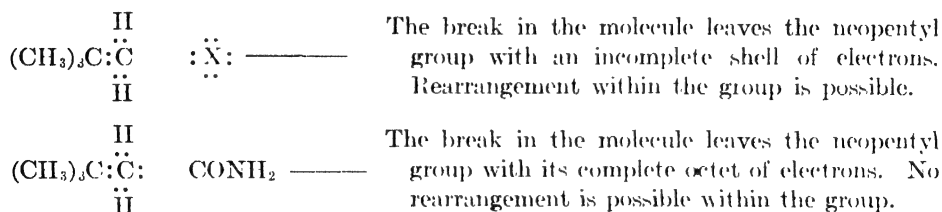
of the type $\text{R}:\ddot{\text{C}}:\ddot{\text{C}}:\ddot{\text{X}}:$ by the action of such halogenating agents as

hydrogen bromide, phosphorus pentabromide, or thionyl chloride on the corresponding carbinol. In these reaction processes the group is deprived of an electron pair, and rearrangement within the system can then take place.

This point of view suggests that if reactions are carried out on these molecules in such a manner as to remove X without its shared pair of electrons then the group has at all times its full quota of electrons, and rearrangement is not possible. In this connection the rearrangement of certain derivatives of β,β,β -triphenylpropionic acid is of special interest. Hellerman⁹³ has shown that the bromamide and the potassium salt of the benzoyl derivative of the hydroxamic acid rearrange under suitable conditions to give β,β,β -triphenylethylamine. The process is accompanied by no rearrangement within the triphenylethyl group.



Whitmore and Homeyer⁹⁴ have studied the Hofmann rearrangement of *tert*.-butylacetamide. This compound yields neopentylamine quantitatively. No rearrangement takes place within the neopentyl group. These investigators picture this striking difference in the behavior of this group in different classes of compounds on the following basis:

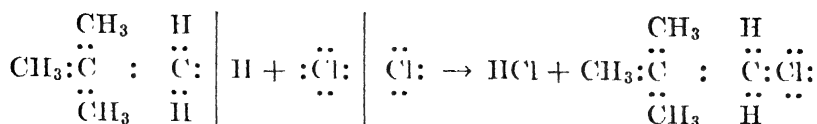


The application of these principles has suggested a method for the preparation of *tert*.-butylmethyl chloride (neopentyl chloride). It has been shown above that it is not possible to obtain this type of compound by the action of the common halogenating agents on *tert*.-butylcarbinol. However, if the substitution is carried out so as to leave the neopentyl group with its full quota of electrons it should be possible to prepare this primary chloride. This task has been accomplished by Fleming and Whitmore.⁹⁵ The chlorination of 2,2-dimethylpropane (neopentane) yields this halide.

⁹³ Hellerman, *ibid.*, **49**, 1735 (1927).

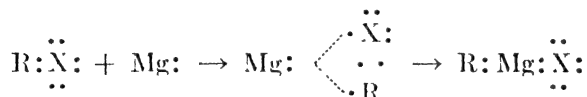
⁹⁴ Whitmore and Homeyer, *ibid.*, **54**, 3435 (1932).

⁹⁵ Fleming and Whitmore, *ibid.*, **54**, 3460 (1932).



It is of interest to note that after it is formed neopentyl chloride is a surprisingly stable chloride. However, it can be stated with certainty that, if metathetical reactions are carried out on it in such a manner as to remove the chlorine atom with its shared pair of electrons, rearrangement products will invariably result.

Whitmore has cited as further evidence for this concept the fact that no rearrangement to tertiary butyl compounds takes place when isobutyl bromide is converted to isobutyl alcohol by the action of oxygen on the Grignard compound.⁹⁶ This failure to yield rearrangement products is interesting when it is remembered that in most metathetical reactions involving isobutyl compounds a change to *tert*-butyl derivatives easily takes place. If the generally accepted hypothesis is adopted that in the formation of the Grignard reagent the reaction takes place in such a way as to involve momentarily a scission of the molecule $\text{R}:\ddot{\text{X}}:$ into the system of potentially neutral free radicals $\text{R}\cdot\cdots\cdot\ddot{\text{X}}:$, then the failure to give products of rearrangement is understood, and is to be expected.



On the basis of this electronic mechanism it is only when the radical is left momentarily with an incomplete sextet of electrons that one should expect it to undergo rearrangement.

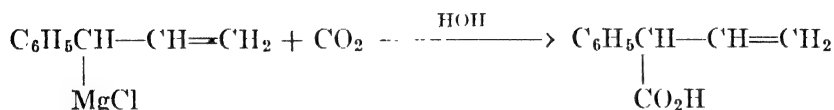
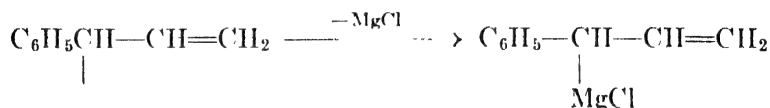
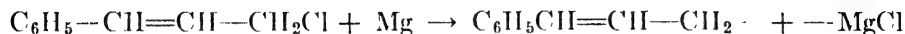
The reader should not get the impression from this discussion that no rearrangements involving the Grignard reagent have been recorded in the chemical literature. Many such rearrangements are on record. However, it is probable that rearrangement occurs during those reaction processes which take place after the formation of the Grignard reagent, and not during the course of the formation of the alkyl- or arylmagnesium halide itself. For example, Gilman and Harris⁹⁷ have observed that the Grignard compound prepared from cinnamyl chloride, $\text{C}_6\text{H}_5\text{CH}=\text{CH}-\text{CH}_2\text{Cl}$, reacts chiefly to give products of the type

⁹⁶ Whitmore and Lux, *ibid.*, **54**, 3448 (1932).

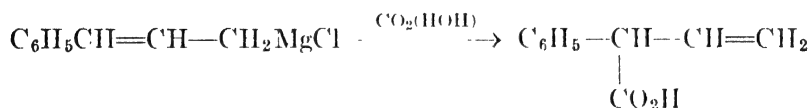
⁹⁷ Gilman and Harris, *ibid.*, **53**, 3541 (1931); Gilman and Kirby, *ibid.*, **54**, 345 (1932) Austin and Johnson, *ibid.*, **54**, 647 (1932).

$\text{C}_6\text{H}_5\text{CH}-\text{CH}=\text{CH}_2$. One of their several interpretations involves the
 $\begin{array}{c} | \\ \text{X} \end{array}$

intermediate formation of free radicals. (See also p. 516).



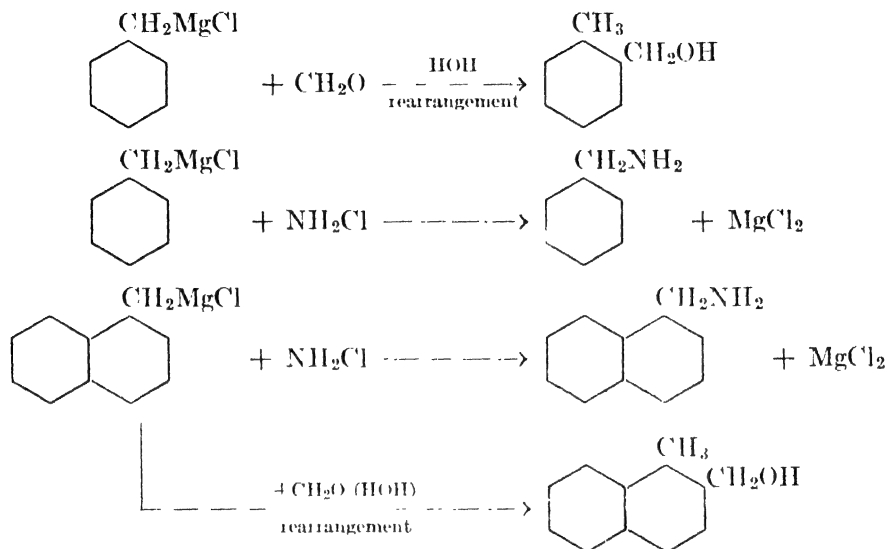
This particular interpretation is unlikely on the basis of the electronic mechanism outlined above. This concept would have one view the rearrangement as taking place after the formation of the Grignard reagent.



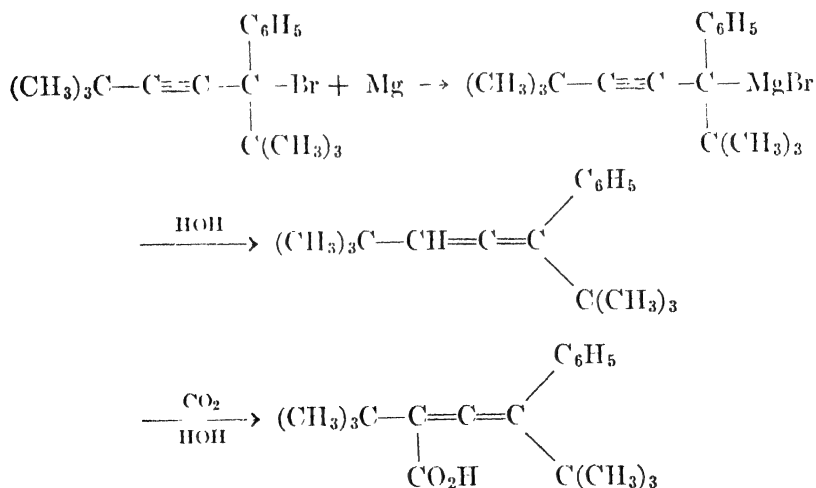
Evidence for this latter formulation is found in the behavior of the Grignard reagent prepared from benzyl chloride. It has previously been seen that in some of its reactions this compound yields products which are formed by processes involving molecular rearrangements. Other illustrations⁹⁸ could be given, as for example the action of formaldehyde, benzaldehyde, ethyl chlorocarbonate, and acetyl chloride on benzylmagnesium chloride. It also gives in some cases the normal and expected product. Coleman and Forrester⁹⁸ have observed that monochloroamine reacts with benzylmagnesium chloride to give benzylamine. No indication of the formation of the rearrangement product, *o*-toluidine, was noted. They also studied the action of monochloroamine on α -naphthylmethylmagnesium chloride. Similar results were obtained, although it is known that in some of its reactions this Grignard compound reacts abnormally. Therefore, it must be assumed, at

⁹⁸ Coleman and Forrester, *ibid.*, **58**, 27 (1936).

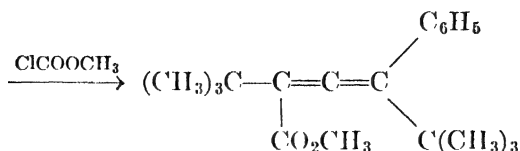
least in these reactions, that the normal Grignard reagent is first formed, and that rearrangement occurs in the reactions which follow.



Another example may be profitably cited. Ford, Thompson, and Marvel⁹⁹ have studied rearrangements of polyynes. They have reported that when the Grignard reagent of phenyl-*tert*.-butyl-*tert*.-butyl-ethynylbromomethane is treated with water, carbon dioxide, or methyl chlorocarbonate the resulting product is an allene derivative. They have formulated the reaction as taking place in the following manner:

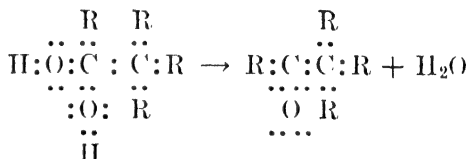
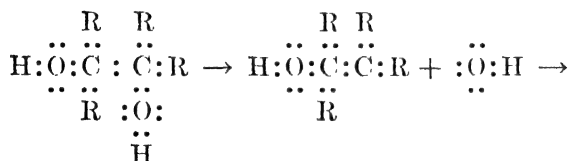


⁹⁹ Ford, Thompson, and Marvel, *ibid.*, **57**, 2619 (1935).



Thus, this interpretation would appear to be in agreement with the concept under discussion.

The electronic mechanism has been used with marked success to explain the various products formed in the dehydration of alcohols. It has been previously pointed out that according to Lachman^{45, 46} the changes involved in the pinacol and allied rearrangements are essentially oxidation-reduction processes which involve a transference of electrons within the molecule. According to Whitmore⁹² this process takes place in the following manner. "The more reactive hydroxyl . . . is removed in the course of the reaction, leaving an open sextet which is completed by a rearrangement."



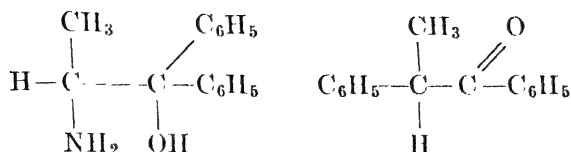
The rearrangement of the iodohydrins follows a similar course.

It should be noted at this point, however, that it has been pointed out both by Wallis and Whitmore¹⁰⁰ and by Bartlett and Pöckel¹⁰¹ that the open sextet actually never does exist as such, for the removal of the hydroxyl group with its electron pair and the rearrangement of the radical, R, occur simultaneously. Bartlett has further concluded that in rearrangements of this type as well as in the Wagner-Meerwein transformations the migrating group approaches its new carbon center from the rear, and thus produces an inversion of configuration when optically active compounds of these types are allowed to rearrange. Bernstein and Whitmore¹⁰² have considered this point of view in their analysis of the semi-pinacolic deamination of dextrorotatory 1,1-diphenyl-2-amino-1-propanol to methylphenylacetophenone

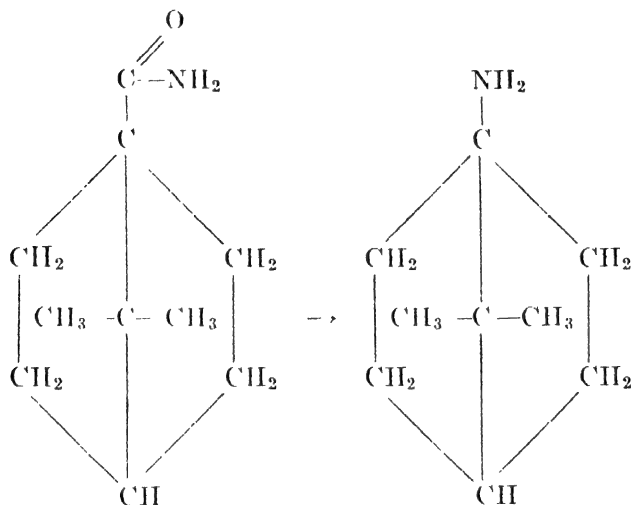
¹⁰⁰ Wallis and Whitmore, *ibid.*, **56**, 1427 (1934).

¹⁰¹ Bartlett and Pöckel, *ibid.*, **59**, 820 (1937).

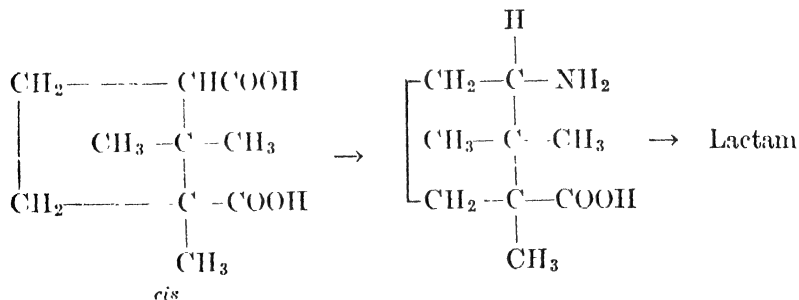
¹⁰² Bernstein and Whitmore, *ibid.*, **61**, 1324 (1939).



If it is to be assumed that in rearrangements of the Curtius, Lossen, and Hofmann types the transformation occurs with retention of configuration then their experiments clearly indicate that Bartlett's views are correct. That retention of configuration during the Hofmann rearrangement can occur in hindered systems has been demonstrated by Bartlett and Knox¹⁰³ in the following series of reactions:

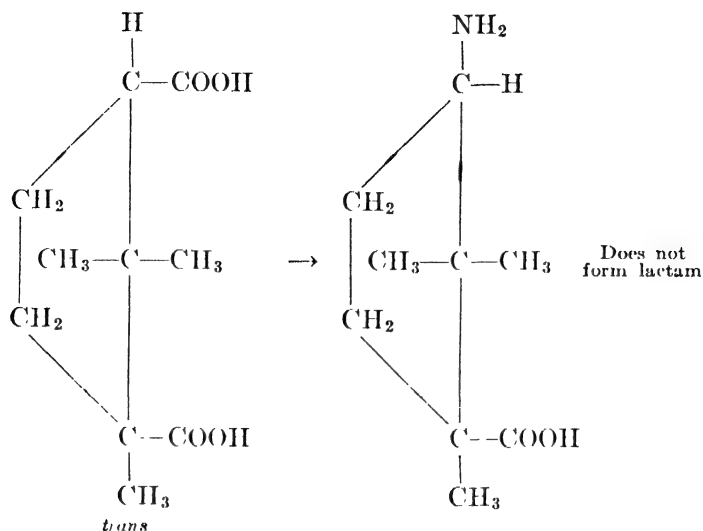


Noyes¹⁰⁴ has also described experiments leading to a similar conclusion in his studies of the degradation of the camphoric acids.

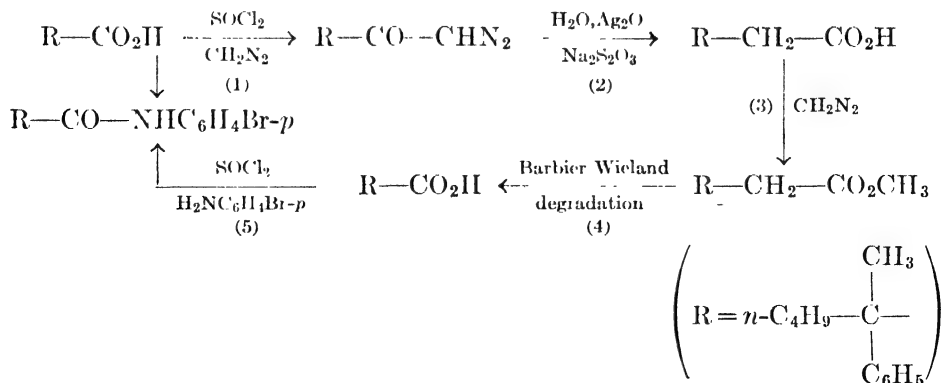


¹⁰³ Bartlett and Knox, *ibid.*, **61**, 3184 (1939).

¹⁰⁴ Noyes, *Am. Chem. J.*, **16**, 500 (1894); Noyes and Porter, *J. Am. Chem. Soc.*, **37**, 189 (1915); **34**, 1067 (1912); Noyes and Nickell, *ibid.*, **36**, 118 (1914).



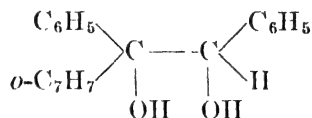
It is to be mentioned that in this case the rearrangement has been carried out under asymmetric conditions and that consequently other directive forces may come into play. In the interest of generality it would be desirable to establish a rigid configurational relationship in the system $\text{R}_1\text{R}_2\text{R}_3\text{C}-\text{COOH} \rightarrow \text{R}_1\text{R}_2\text{R}_3\text{C}-\text{NH}_2$. Only then would it be possible to state with certainty that the Hofmann rearrangement always occurs with retention of configuration. The essential point in question, namely whether in the absence of special directive forces an asymmetric carbon atom can preserve its configuration when it migrates with an electron pair from A to B, has been rigorously proved, however, in the investigations of Lane and Wallis¹⁰⁵ on the Wolff rearrangement of optically active diazoketones, for in this case the necessary configurational relationships are readily obtainable. The proof was achieved by the following cyclic process:



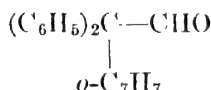
¹⁰⁵ Lane and Wallis, *ibid.*, **63**, 1674 (1941).

Since only step 2 in this cycle involved the breaking of a bond of the asymmetric center, it is clearly established that in this step the Wolff rearrangement proceeded without a Walden inversion. The assumption of Bernstein and Whitmore seems, therefore, to be justified.

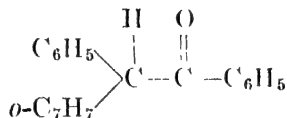
It is fitting to point out that these views of an electronic mechanism outlined in the preceding pages have certain limitations. For example, they need to be extended to explain the results of McKenzie, Roger, and McKay,¹⁰⁶ in their studies on the pinacol rearrangement of optically active 1,2-diphenyl-1-*o*-tolylethanol, diol,



Dehydration with dilute sulfuric acid gives an aldehyde,

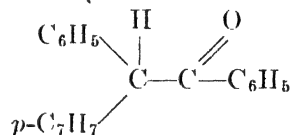


and an optically active ketone



In striking contrast to these results are those obtained with the corresponding optically active modifications of 1,2-diphenyl-*p*-tolylethane-diol-1,2. This compound behaves differently. No aldehydes are formed

on rearrangement, and the *p*-tolyldeoxybenzoin,



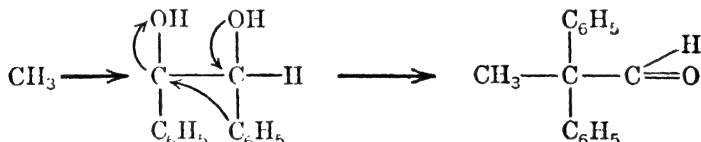
which is formed is completely inactive when either oxalic acid, cold sulfuric acid, or hot dilute sulfuric acid is used as the dehydrating agent. At first glance this apparent disparity in results is hard to understand. However, reflection will show that there are good reasons for these differences in their observations. If we recall the strengths of the acids, *o*-toluic acid (*a*), benzoic acid (*b*), *p*-toluic acid (*c*), we find that (*a*) is stronger than (*b*) and that (*c*) is weaker than (*b*). In terms of electrons we may construct a picture in which the methyl group in the *para*-position is electron repelling and in the *ortho*-position is electron attracting.

¹⁰⁶ McKenzie, Roger, and McKay, *J. Chem. Soc.*, 2597 (1932); Roger and McKay, *ibid.* 332 (1933).

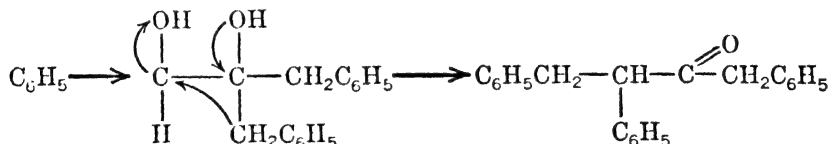
quantitative correlation is true only where the variable group is in the acid portion of the molecule.

The electronic mechanism as outlined has other limitations. It does not aid one in predicting the nature of the products formed when the groups attached to the two central carbon atoms of the pinacol are different. However, Ingold¹⁰⁸ has treated this problem also from the electronic viewpoint and has come to certain conclusions which are of interest. According to him, in compounds of the type $RR_1C(OH)C(OH)R_2R_3$, the nature of the ketone which is formed will depend on the particular hydroxyl group which is eliminated as water during the reaction process. This elimination in turn depends on the capacity for electron release of the groups which are attached to the two central carbon atoms. The hydroxyl group will be removed from that carbon atom whose groups have the greatest capacity for electron release. Ingold¹⁰⁸ points out that this capacity may be derived from theoretical considerations or may be obtained from observations in other fields of organic chemistry. From the vast amount of data which is available he has established the relationship: $H < \text{alkyl} < \text{aryl}$, in which hydrogen has the least capacity for electron release. For purposes of illustration he has formulated these changes in the following manner:

(a) $H < \text{alkyl}$ (CH_3 , C_2H_5)



(b) $\text{alkyl} < \text{aryl}$ (C_6H_5 , etc.)



Many other compounds involving rearrangements of this type have been discussed by him from this point of view, but the principles involved are essentially the same. It is sufficient at this time to state that the rearrangements of ethylene oxides apparently follow similar rules, and that these compounds yield either of two ketones according to the relative capacities of the groups for electron release. However, it would appear that in some instances there are exceptions. Lévy and Sfras¹⁰⁹

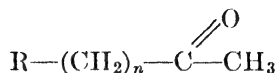
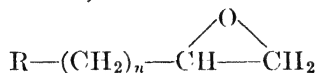
¹⁰⁸ Ingold, *Ann. Repts. Chem. Soc. (London)*, **25**, 124-134 (1928).

¹⁰⁹ Lévy and Sfras, *Compt. rend.*, **184**, 1335 (1927).

have studied the rearrangement of some ethylene oxides of the type $C_6H_5(CH_2)_n-CH-CH_2$ [$n = 1$ to 4]. They report that on rearrangement

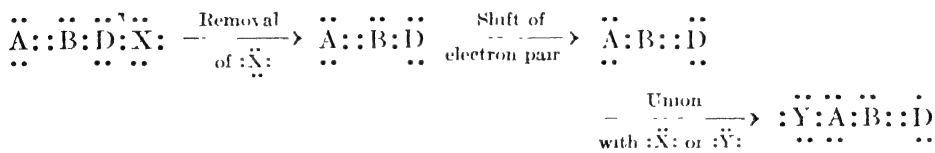


the hydrogen atom migrates in preference to either the benzyl group, the phenylethyl group, the phenylpropyl group, or the phenylbutyl group. Thus,

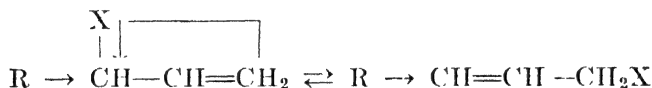


It must be stated, however, that these rearrangements were carried out under drastic conditions. The isomerization was produced by heating the oxides with zinc chloride, or by passing the vapors over alumina at 260°. Therefore, their results may be explained on the assumption that under such conditions a further isomerization of the primary product takes place.¹¹⁰

Interesting application of the electronic concept has been made to allylic systems. Whitmore⁹² formulated the change:



The case $X = Y$ (triad anion tautomerism) has been similarly discussed by Ingold for systems:

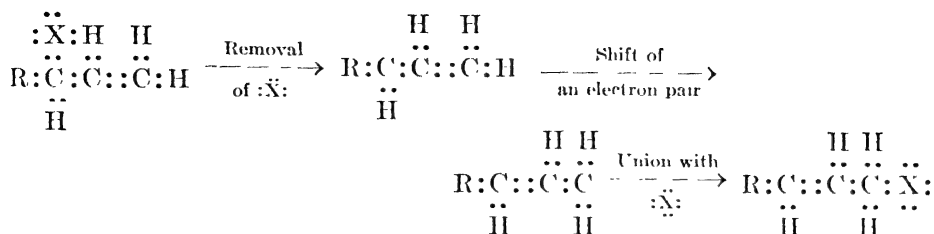


Here also the case with which the anion X leaves the system depends in part on the capacity of the group R for electron release, that is, to supply electrons to the "depleted" carbon atom. A study of a number of such systems where R is *p*-chlorophenyl, *p*-tolyl, phenyl, methyl, etc., shows that the order is



Ingold also points out that, in all these systems, X will take its position "adjacent to the least activating of the terminal groups." The particular type of triad anion tautomerism, ($X = Y$), discussed in the preceding paragraph would be formulated as follows:

¹¹⁰ Bennett and Chapman, *Ann. Repts. Chem. Soc. (London)*, **27**, 117 (1930).



It is to be noted that, in Whitmore's formulation, the exchange of Y for X in either $\text{:}\ddot{\text{A}}::\ddot{\text{B}}:\ddot{\text{D}}:\ddot{\text{X}}:$ or $\text{:}\ddot{\text{X}}:\ddot{\text{A}}:\ddot{\text{B}}::\ddot{\text{D}}$ should lead to the same products $\text{:}\ddot{\text{Y}}:\ddot{\text{A}}:\ddot{\text{B}}::\ddot{\text{D}}$ or $\text{:}\ddot{\text{A}}::\ddot{\text{B}}:\ddot{\text{D}}:\ddot{\text{Y}}:$ or to the same mixture of these two, since, regardless of which compound is taken, the reaction must proceed through the resonating pair of intermediates $\ddot{\text{A}}::\ddot{\text{B}}:\ddot{\text{D}}:$, $\ddot{\text{A}}:\ddot{\text{B}}::\ddot{\text{D}}$. The equilibrium value of this resonance will determine the composition of the final product.

That this is substantially correct was found by Young and Lane¹¹¹ in their work on the conversion of crotyl alcohol and methylvinylcarbinol to the corresponding butenyl bromides under conditions preventing tautomerization of the bromides following their preparation. It was found that the equilibrium mixture of bromides expected on the basis of such a mechanism constituted from 88 to 97 per cent of the final product, the remaining product being the isomeric bromide corresponding to the alcohol used. The percentage of reaction proceeding by such a mechanism was determined by the activity of the hydrogen bromide in the solution and approached 100 per cent in dilute hydrobromic acid solution. The composition of the equilibrium mixture of bromides was also markedly affected by the acid concentration.

This interpretation of the electron changes which take place within these systems has the advantage of clearness, and of freedom from abstractness and variety of detail. It must be remembered, however, that here, as in other cases which have previously been discussed, such a mechanism tells one nothing of the effect of the group R on the ease of rearrangement. Herein lies its weakness, and for such information more experimental facts are needed.

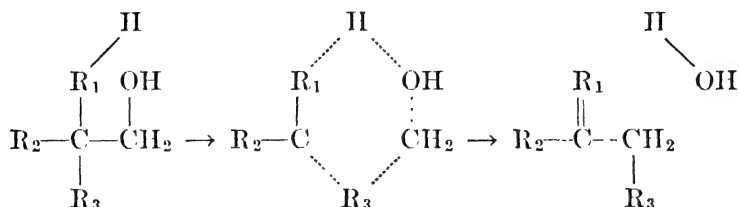
The electronic mechanism has been used to explain the Wagner rearrangement of *tert*-alkylcarbinols. Ingold^{108, 112} uses the same principles of electron displacement as have been outlined above. A closely analogous interpretation has also been given by Robinson,¹¹³ in which

¹¹¹ Young and Lane, *J. Am. Chem. Soc.*, **59**, 205 (1937); **60**, 847 (1938).

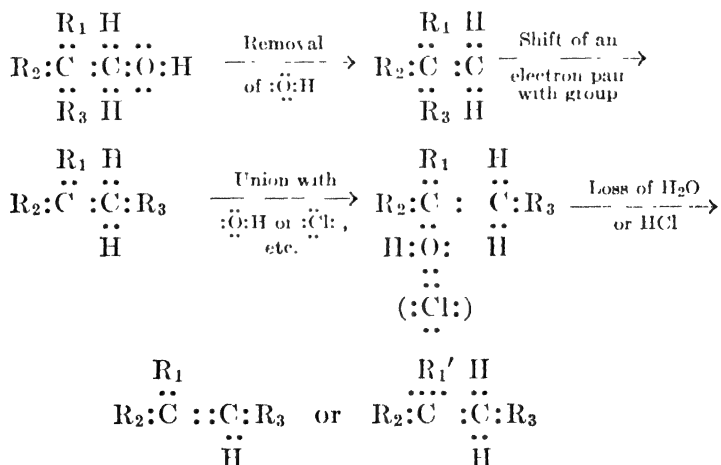
¹¹² Burton and Ingold, *J. Chem. Soc.*, 904 (1928); Ingold and Smith, *ibid.*, 2752 (1931); Ingold and Shoppee, *ibid.*, 1199 (1929).

¹¹³ Robinson and co-workers, *J. Soc. Chem. Ind.*, **44**, 456 (1925); *J. Chem. Soc.*, 1610, 1619 (1925); *ibid.*, 401 (1926).

his earlier theories involving partial valencies have been reëxpressed in terms of electronic displacements equivalent to the polar partial valency symbols previously used. The reaction studied by Wallis and Bowman⁸¹ may serve as an illustration of this transformation. In terms of an electronic mechanism based upon the principles of Jones, Stieglitz, and Whitmore, at least for that portion which gives rise to an optically active product, the reaction may be formulated in the following manner:



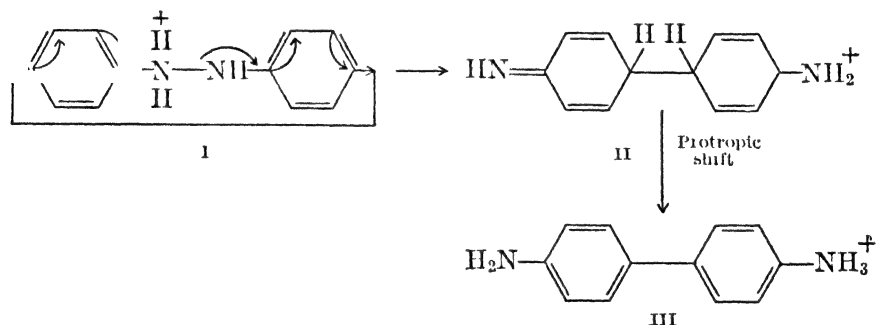
It is to be remembered, as has been stated previously, that this mechanism implies that the hydrocarbon radical supplying the hydrogen atom eliminated as water is not the radical which migrates to the adjoining carbon atom. In this respect it is in effect opposed to that of Ruzicka.¹¹⁴ There are instances, however, of this type of rearrangement in which no water is eliminated during the rearrangement process. The reaction studied by Wallis and Bowman⁷⁴ is an illustration of the point under discussion. Therefore, it would seem that an electronic mechanism based on the principles of Jones, Stieglitz, and Whitmore more nearly represents the true picture of the reaction process at least for that portion which gives rise to an optically active product. In terms of these concepts the reaction would be formulated in the following manner:



¹¹⁴ Ruzicka, *Helv. Chim. Acta*, **1**, 130 (1918); Ruzicka and Liebl, *ibid.*, **6**, 267 (1923); see, also, Zumpfe, *Monatsh.*, **25**, 124 (1904).

Similar mechanisms have been proposed by Whitmore⁹² to explain the nature of the products formed in the dehydration of other types of alcohols.

An electronic mechanism may be used with success to explain various other types of intramolecular rearrangements. For example, Ingold¹¹⁵ has recently studied the benzidine rearrangement, and has found it to be an intramolecular process. It is pertinent that brief description of his method be given. Two benzidine transformations were carried out in the same homogeneous solution. Two hydrazobenzene derivatives were selected which would undergo rearrangement at comparable speeds, and which were also of such a nature as to insure a benzidine conversion without a simultaneous semidine isomerization. It was found that, when mixed in equimolecular concentrations and allowed to rearrange, each acted independently of the other, and that no mixed benzidine was formed. From these results Ingold concluded that there was no separation of groups either as ions or as radicals. Before the nitrogen link is broken the *para*-positions must come within each other's sphere of influence. The rearrangement takes place within the molecule. He explains these facts on the basis of the following formulation:



This particular description of the reaction process has recently been criticized by Robinson,¹¹⁶ who points out that, if the complex (II) really were an intermediate, then such imine salts should readily hydrolyze to give phenols and ammonia, two products which have not been observed in this rearrangement. Moreover, when this formulation is applied to *p,p'*-disubstituted hydrazobenzenes compounds of the type

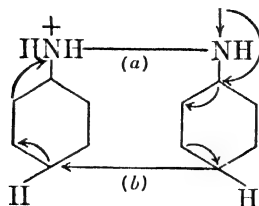


should be produced. This also never happens. Therefore, Robinson proposes the following:

¹¹⁵ Ingold and Kidd, *J. Chem. Soc.*, 984 (1933).

¹¹⁶ Robinson, "Presidential Address," *J. Chem. Soc.*, 220 (1941).

1. First phase

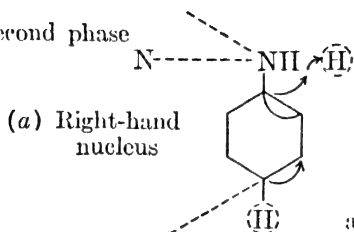


(a) is a "full one-electron make or break of a covalency."

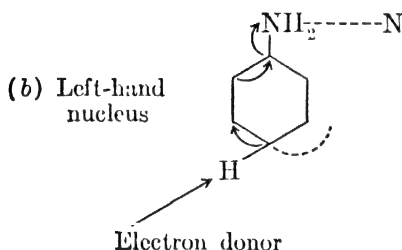
The arrows are displacements of very small extent relative to (a).

(a) and (b) are irreversible.

2. Second phase



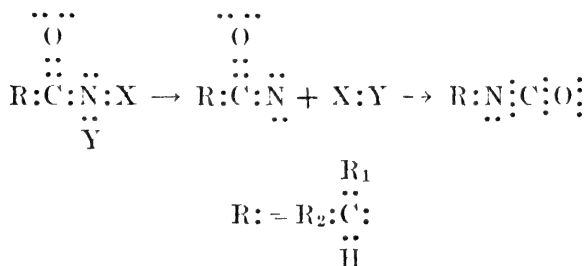
anionoid complex (i.e., electron donor).



These changes relieve the strain in the electromeric system without reversing the first phase and insure the preservation of the aromatic character of both nuclei. The simultaneous operation of both phases constitutes a process of intramolecular oxidation and reduction which leads directly to the formation of the benzidinium salt (III). The hydrazo group is reduced by the electrons which pass through the conducting aromatic nuclei. The *para*-positions at the same time lose two protons and two electrons, and become oxidized. Robinson¹¹⁶ has also applied this mechanism to the semidine rearrangement and certain other oxidation processes.

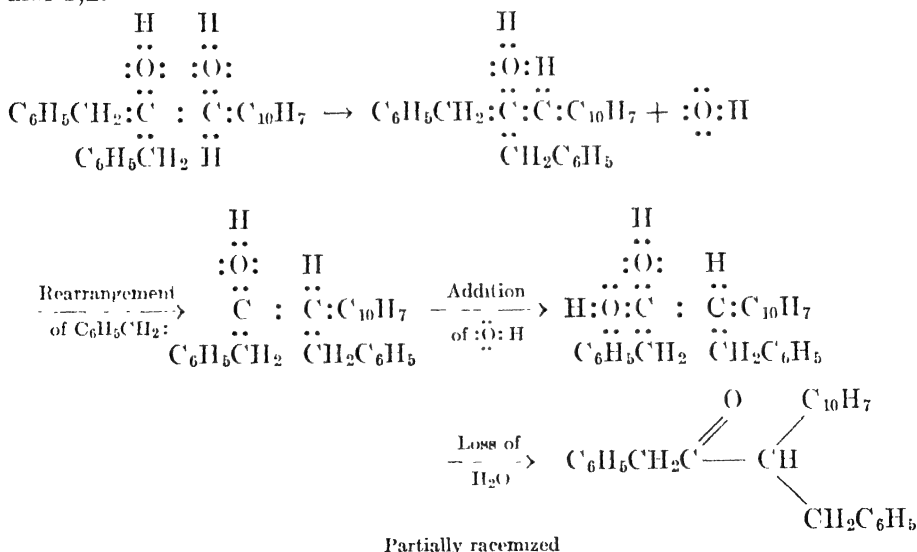
The application of this concept to intramolecular rearrangements gives us an explanation of certain other interesting facts. In a study of certain intramolecular rearrangements involving optically active radicals, notably of the Curtius, Hofmann, and Lossen types, it has been shown that not only does the optically active group maintain an asymmetric configuration during the rearrangement but also that no appreciable racemization occurs during such transformations. These facts are significant in view of the presence of partial or complete racemiza-

tion always observed in the rearrangements of optically active pinacols, alkyl phenyl ethers, and *tert*-alkylecarbinols. On the basis of an electronic mechanism this difference in the optical stability of the tricovalent groups is to be expected. The electronic nature of the group containing the asymmetric carbon atom is different in the two classes of rearrangements. In the former case, according to the ideas of Stieglitz^{25, 30, 35} and of Whitmore,³² the rearrangement process involves a shift of an electron pair with its attached group. Thus at no time is the asymmetric carbon atom without its full quota of electrons.



In rearrangements of pinacols, and *tert*-alkylecarbinols, however, the optically active group is deprived momentarily of an electron pair.

Pinacol rearrangement of 3-phenyl-2-benzyl-1-naphthylpropane-1,2-diol-1,2.

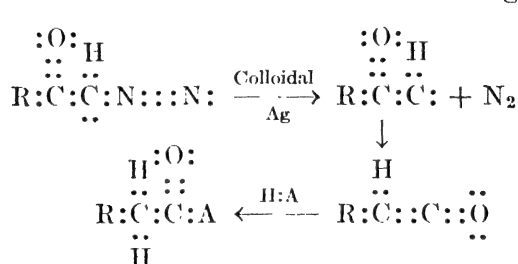


Therefore, its electronic nature is different and it should not be anticipated, even though the migrating group is never free, as the results of Wallis and Moyer⁴¹ have shown, that such a group with a sextet of

electrons would have as great optical stability as one in which the asymmetric carbon atom has at all times its complete octet of electrons.

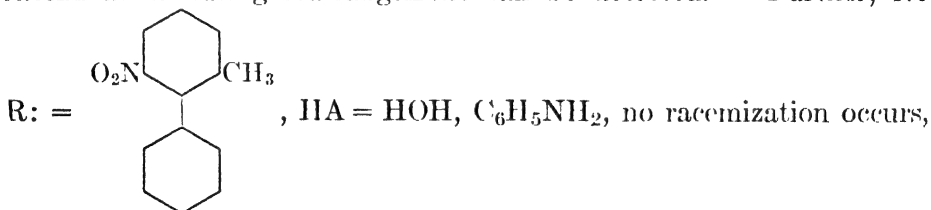
Recent considerations of the Wolff rearrangement give further support to these views. This reaction has long been regarded as analogous

to the Curtius type of rearrangement, the shift of a $\text{—C}=\text{N}<$ fragment in the latter process being formally replaced by the fragment $\text{—C}=\text{C}<$. Thus Arndt and Eistert¹¹⁷ have formulated the rearrangement as follows



where A is OH^- , OEt^- , NH_2^- , NHC_6H_5 , etc.

Since the second step is regarded as involving a shift which leaves the radical R always in full possession of its electron pair, it is to be expected that on the basis of this formulation an optically active group will maintain its asymmetry throughout the process just as in the preceding case. This conclusion is substantially in agreement with experiment. When R: = $(\text{C}_6\text{H}_5)(\text{CH}_3)(n\text{-C}_4\text{H}_9)\text{C}$: HA = HOH, $\text{C}_6\text{H}_5\text{NH}_2$, no racemization during rearrangement can be detected.¹¹⁸ Further, for



a result which is wholly in accord with the work of Wallis and Moyer⁴¹ on the Hofmann rearrangement, and which supports the intramolecular interpretation of both types of rearrangement.

It is to be noted, however, that, when R: = $(\text{C}_6\text{H}_5\text{CH}_2)(\text{CH}_3)\text{HC}$: HA = HOH, $\text{C}_6\text{H}_5\text{NH}_2$, complete racemization occurs, while for HA = HNH_2 partial racemization results.¹¹⁹ These facts are surprising considering that the stability of the same radical in rearrangement of the Curtius type is very probably to be attributed to an enolization of

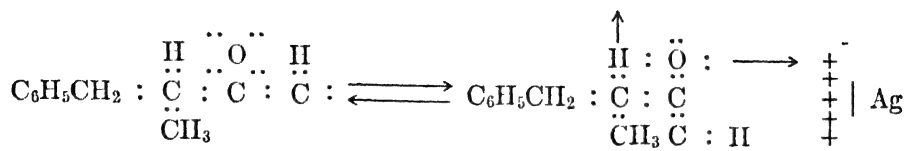
¹¹⁷ Arndt and Eistert, *Ber.*, **68**, 200 (1935).

¹¹⁸ Lane and Wallis, *J. Org. Chem.*, **6**, 443 (1941).

¹¹⁹ Lane, Willenz, Weissberger, and Wallis, *ibid.*, **5**, 276 (1940).

the intermediate $\text{C}_6\text{H}_5\text{CH}_2:\overset{\text{H}}{\underset{\text{CH}_3}{\text{C}}}:\overset{\text{O}}{\text{C}}:\overset{\text{H}}{\text{C}}:$ facilitated perhaps by the silver ion

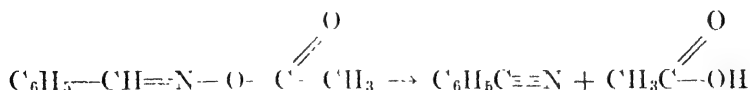
in conjunction with the catalytic silver surface always present in these reactions, i.e.,



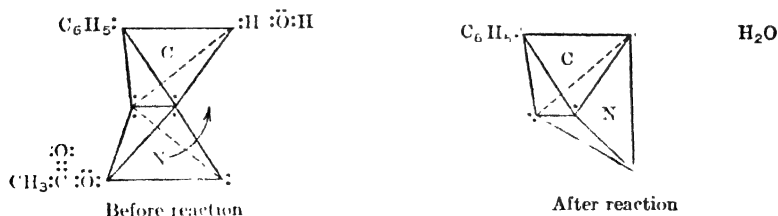
rather than to any essential difference in the electronic behavior of the benzylmethylecarbinyl radical during the migration process.

Before concluding this discussion of the electronic concept as an explanation of intramolecular rearrangements it is appropriate to consider its application to certain stereochemical problems which are involved in the chemistry of the isomeric oximes. Jones, Stieglitz, Lachmann, and Whitmore, whose ideas have been discussed in the preceding paragraphs, have not applied their electronic concepts to problems dealing with the phenomenon of *cis* or *trans* elimination of radicals or of *cis* or *trans* migration of radicals in geometrical isomers. The ideas of Mills,¹²⁰ however, are of special interest in this connection.

It will be recalled that an easy method of converting benzaldoximes into the corresponding nitriles is by the action of aqueous sodium carbonate solution on the acetyl derivative of the aldoxime.



With the aid of the tetrahedral model and of the electronic concept, Mills formulates this change as follows:



Thus, it can be seen that the products are water, benzonitrile, and the acetate ion. According to him the liberation of these components which are already present in the acetyl derivative constitutes a second-

¹²⁰ Mills, *Chemistry & Industry*, **51**, 755 (1932).

ary reaction and is the result of a direct action of the sodium carbonate solution. The primary reaction is the removal of a proton by the hydroxide to form water.

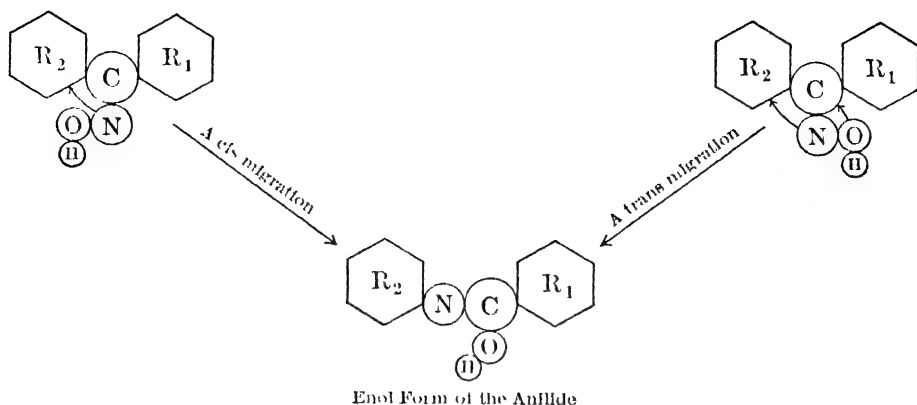
Mills describes the sequence of changes as follows: "The elimination of acetic acid consists of a chain of three events, each dependent on the next. The first is the removal of a proton. The second is the movement of the nitrogen nucleus to bring it into alignment with the phenyl-carbon valency. The third, which is the immediate consequence of the second, is the liberation of the acet-ion.

"The determining factor which causes the unequal readiness of *cis* and *trans* elimination is the linear configuration of benzonitrile. The centers of the carbon and nitrogen atoms of the cyanogen group, and of the carbon atom of the phenyl group to which it is attached, lie in a straight line. The formation of benzonitrile therefore entails the movement of the nitrogen nucleus in the direction shown."

In discussing this sequence of events Mills points out that in the acetates of *trans*-aldoximes this movement aids the liberation of the acetate ion since its direction is away from the acetoxy group. In the acetates of the corresponding *cis*-aldoximes the movement of nitrogen atom does not give the acetoxy group equal opportunity to escape as the acetate ion. Therefore, since each step in the chain of events is dependent on the next, it follows that in the acetates of the *cis*-aldoximes the tendency to give up a proton to the alkaline solution is less. Consequently these acetates are less acidic, and dehydration is more difficult. Thus, Mills' application of the electronic concept leads to the conclusion that the configurations formerly assigned to the aldoximes have to be interchanged. This is in agreement with the more recently discovered facts.

Similar relationships hold for the ketoximes. The work of Meisenheimer has shown that in the Beckmann rearrangement the radicals which migrate do not lie on the same side of the C'N group. Here, also, it has been necessary to interchange the configurations which were formerly given to these isomeric compounds. Mills has proposed an interesting explanation of how a *trans*-migration of the group occurs.

In the preceding sections of this chapter the phrase "migration of the group" has often been used. Such terms are generally employed. Mills points out, however, that if isolated molecules are considered, and it is remembered that in nature moment of momentum is conserved, then it becomes obvious that very often most of the movement involved in a rearrangement is not made by the group but by a particular atom.¹²⁰ In the oximes it is the nitrogen atom which probably undergoes displacement. Mills represents this change as follows:



With the aid of such a diagram it may be seen at a glance that the *trans*-migration is much more probable.

This formulation of the rearrangement process, however, is open to certain valid criticisms. It must be remembered that the argument of Mills, that the total moment of momentum for a molecule must be conserved in a reaction, is true only for a single molecule which is far away from other molecules and from the walls of the reaction vessel. In the presence of these other molecules no such principle holds, and therefore conclusions drawn from it have only accidental validity. Even for an isolated molecule the usefulness of this principle is very questionable, for if the only condition of rearrangement lay in conserving the total moment of momentum then it would be possible to bring about any kind of internal rearrangement one desired. Since this is not possible it would seem that a more fundamental principle is involved.

APPLICATION OF THE MODERN THEORY OF REACTION RATES TO THE STUDY OF INTRAMOLECULAR REARRANGEMENTS

It is now well established that the factor which in reality determines whether a molecule can or cannot undergo chemical reaction is the amount of internal energy which it possesses. In concluding this chapter it seems fitting to discuss briefly, in the way which has been found to be so effective in physical chemistry, the application of this principle to reaction processes.

The chief data used by chemists in determining structure are the type reactions which the molecule undergoes. In the past the organic chemist has been satisfied with a knowledge of the configuration of stable molecules, that is, the relative positions of the atoms, and in some instances their interatomic distances. This situation, however, is now changing rapidly, and at the present time it is possible to understand

reactions in a way which was not possible a very few years ago. One example will serve to illustrate the point.

If, in addition to the relative positions of the atoms in a molecule and their distance apart, one also knows their vibration frequencies and the heat of reaction for a chemical process, it is now possible to calculate the equilibrium constant for the reaction. This has been done already for many organic molecules,¹²¹ and the procedure is becoming of increasing importance not only to those who wish to understand the fundamental principles of chemistry, but also to those who wish to apply them.

The modern theory of reaction rates in the form proposed by Eyring,¹²² and applied by him and his co-workers to several reaction processes, proceeds along entirely similar lines. According to Eyring, even for very complicated reactions involving one or many molecules, "there is some stage (or stages if it be a chain reaction) which is slowest, and, therefore, is the rate-determining process." He calls this stage the activated state, and the arrangement of the atoms in this state he designates as the activated complex. Applying the principles involved in chemical equilibria,¹²³ if one knows the distance between the atoms, their vibration frequencies, and the energy of the activated state as compared with the initial state, one can calculate the corresponding equilibrium constant K^\ddagger for the activated complex. Since this complex decomposes at the rate kT/h , the specific reaction rate, k' , for the reaction is given by the equation

$$k' = \frac{\mathcal{H} K^\ddagger kT}{h} \quad (1)$$

where \mathcal{H} is the chance that a molecule has of decomposing by passing once through the activated state, and k , T , and h are Boltzmann's constant, the absolute temperature, and Planck's constant, respectively. It is at once obvious that since the activated complex has a mean life of h/kT which at room temperature is approximately 10^{-13} second it cannot be isolated and examined. Conversely, any intermediate compound which can be isolated cannot even remotely resemble the activated complex. If this is true then any evidence about reaction mechanisms of molecular rearrangements which is based upon isolated intermediate compounds must be examined very critically.

¹²¹ Kassel, *J. Am. Chem. Soc.*, **55**, 1351 (1933); *J. Chem. Phys.*, **4**, 435 (1936); Smith and Vaughan, *ibid.*, **3**, 341 (1935).

¹²² Eyring, *ibid.*, **3**, 107 (1935); Wynne-Jones and Eyring, *ibid.*, **3**, 492 (1935). See, also, Pelzer and Wigner, *Z. physik. Chem.*, **15B**, 445 (1932); Wigner, *ibid.*, **19B**, 203 (1932) Evans and Polanyi, *Trans. Faraday Soc.*, **21**, 875 (1935).

¹²³ Stearn, Ru, and Eyring, private communication.

Since according to the theory of equilibrium

$$K = e^{-\Delta F/RT} = e^{\Delta S/R} \cdot e^{-\Delta H/RT}$$

then we may write equation 1 in the form

$$k' = \frac{kT}{h} e^{-\Delta F^\ddagger/RT} = \frac{kT}{h} e^{\Delta S^\ddagger/R} \cdot e^{-\Delta H^\ddagger/RT} \quad (2)$$

where $\mathcal{K} = 1$ and ΔF^\ddagger , ΔS^\ddagger and ΔH^\ddagger are the standard increases in free energy, entropy, and heat content, respectively, when the activated complex is formed from the reactants. ΔH^\ddagger can thus be obtained from the relation

$$\Delta H^\ddagger = RT^2 \frac{d \ln k'}{dT} - RT \quad [\text{differential form of (2)}]$$

ΔH^\ddagger and k' being known, ΔS^\ddagger can be evaluated.

It is possible in principle to evaluate ΔH^\ddagger and ΔS^\ddagger from spectroscopic data, but, except for a few simple reactions, such a procedure, which is quite laborious, is not at present satisfactory. The present usefulness of equation 2 in organic chemistry, therefore, lies more directly in the study of reaction mechanisms. It is also to be pointed out that, for a system which may undergo either of two (or more) reactions resulting in different sets of products, it is frequently true that ΔS^\ddagger is nearly the same for each reaction. This means that the values of k' for the two possible reactions k'_A and k'_B which determine the relative yields will depend on factors which affect the values of ΔH^\ddagger for the two reactions.

Recently Ri and Eyring¹²⁴ have studied the general problem of the nitration of monosubstituted benzenes from this point of view. They accept the general explanation usually advanced in modern organic chemistry as to why some substituents are *ortho*- and *para*-orienting while others are *meta*-orienting. It is to be recalled that this general explanation involves the following two assumptions. (a) By induction and resonance effects an *ortho*- *para*-orienting substituent makes the electron density on the corresponding carbon atoms greater than that on the *meta*-carbon atom. A *meta*-orienting group acts in the opposite manner. (b) Substituting agents are electrophilic, i.e.,¹²⁵ electron-seeking, because of this positive nature. Because of this they react most easily with that carbon atom which is surrounded by the greatest number of electrons.

If this explanation is correct then the percentage yields of *ortho*-, *meta*-, and *para*-compounds, which of course are proportional to the

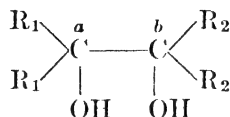
¹²⁴ Ri and Eyring, *J. Chem. Phys.*, **8**, 433 (1940).

¹²⁵ Ingold, *J. Chem. Soc.*, 1120 (1933).

corresponding reaction rates, should provide a means of determining the charge distribution, and hence should permit calculations of the dipole moments of such molecules from rate data alone. If the moments so calculated agree with those observed experimentally the above explanation of the orienting power of substituents would have a more substantial basis, and consequently assumption (b) could be formulated more precisely. Conversely, one could also calculate with justification the relative rates of substitution in *ortho*-, *meta*-, and *para*-positions solely from dipole moments.

By making certain assumptions Ri and Eyring¹²⁶ have done this in the case of the nitration of certain monosubstituted benzenes. By means of the same treatment of the problem Stearn, Ri, and Eyring¹²³ have also been able to throw light on mechanisms involved in molecular rearrangements. It is fitting at this time to discuss such processes from this point of view. The pinacol and Hofmann rearrangements may be chosen for illustration.

These investigators are of the opinion that there are two possibilities for the mechanism of the pinacol rearrangement. Either the hydroxyl group may first be removed, followed by the breaking of the bond holding the migrating radical, or else the two bonds in question break in the reverse order. It seems the more probable that one of the C—OH bonds breaks first. For symmetrical pinacols the two C—OH bonds are equivalent. Therefore, each bond has the same probability of rupture. If such a rupture is the first process then the "migration aptitude" of a particular group will have a significance independent of the molecule as a whole. On the other hand, for unsymmetrical pinacols the nature of the groups will determine largely which of the two C—OH bonds will break the more easily. As a result any relative migration aptitudes of these groups will depend on their arrangement as well as on their individual properties. In the more idealized type cases Eyring and his co-workers have pictured more definitely the mechanisms for the symmetrical and the unsymmetrical pinacols. Taking for the purpose of illustration a molecule in which the groups R_1 and R_2 are of such a nature that R_1 is distinctly more electrophilic than R_2 they state that for the unsymmetrical pinacol



"since R_2 is the stronger electron donor, the carbon to which it is at-

¹²⁶ Ri and Eyring, unpublished results.

tached will have a weaker bond to its oxygen atom than will the other carbon, and thus as a net result, R_1 will migrate predominantly.* If the R_1 groups are different but both more electrophilic than R_2 then the relative amounts of R_1 groups migrating will depend on the individual 'migration aptitude.' It is seen that such a mechanism does not preclude the possibility of some migration of R_2 groups. The given conditions merely assume that the migration of R_1 groups predominates.

"For the symmetrical pinacols, $\begin{array}{c} R_1 \diagup \\ C - \cdots - C \diagdown \\ R_2 \diagdown \quad | \quad | \quad R_1 \\ \quad \quad OH \quad OH \end{array}$, each C'-OH bond

has an equal chance of breaking, and the end result will be the same whichever bond breaks. When the OH splits as an ion at the point indicated by the dotted line, taking with it a proton from the other OH to form water, this will leave a negative charge accumulated on the carbon atom which retains its oxygen, so that now R_2 , being less electrophilic than R_1 , will migrate predominantly. Thus, it will happen frequently that in a symmetrical pinacol one group migrates predominantly whereas in the unsymmetrical isomer another group undergoes the change."

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* "It may happen that if the C'- R_1 bond is very strong the breaking of the C'-OH bond at the *b* carbon atom will not always be followed by migration of R_1 groups. The result will then be that the two C'-OH bonds will tend to become more nearly equivalent as the rate-determining step, and the breaking of the C'-OH from the *a* carbon atom may on occasion predominate with the resulting migration of R_2 ."

CHAPTER 13

COMPARISON OF CHEMICAL REACTIVITY

HOMER ADKINS

University of Wisconsin

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Introduction. From the time that the student of organic chemistry reads an elementary textbook until the day that his contact with the science is broken, he will be under the necessity of comparing the chemical behavior of substances having the same or similar functional groups. The number of carbon compounds is so large and so many of them have similar reactions that he finds it convenient to relate certain types of reaction to certain structures or functional groups. In particular, he finds that the principle of homology enables him to group together large numbers of compounds which behave similarly under specified conditions. However, he realizes as he progresses beyond the most elementary stage that not even homologs show identical reactions, and isomers may even show qualitative as well as quantitative differences in behavior. He thus is driven to make comparisons in the chemical behavior of substances having similar functional groups. It is the purpose of this chapter to give an analysis of the methods whereby the chemical reaction of compounds may be compared and to note some of the simpler relationships of structure and chemical reactivity. An attempt will be made to define what *may be meant* by a statement that compound A is more "stable" or "reactive" than compound B, or that radical A is more "negative" or "positive" than radical B.

Bridgman in his book "The Logic of Modern Physics" develops the thesis that "physical concepts have meaning only in so far as they can be defined in terms of operations." Langmuir¹ in his presidential address entitled "Modern Concepts in Physics and Their Relation to Chemistry" before the American Chemical Society refers to the importance of Bridgman's thesis and discusses its relationship to chemistry, for "Science" might well replace "Physics" in the title of Bridgman's book. Langmuir states that "The progress of modern science depends largely upon (1) giving to words meanings as precise as possible; (2) definition of concepts in terms of operations; (3) development of models (mechanical or mathematical) which have properties analogous to those of the phenomena which we have observed."

The present chapter is an attempt to illuminate steps 1 and 2 of this program so far as it applies to the comparison of the chemical reactivity of organic compounds, for in perhaps no other group of phenomena is it more necessary that a statement of comparison be linked to the operation by means of which the experimental data underlying the statement were obtained.

A comparison of the chemical reactivity of two or more compounds may be made (A) in a system that is at equilibrium or (B) in a system that is not at equilibrium. These two aspects of the problem have

¹ Langmuir, *J. Am. Chem. Soc.*, **51**, 2847 (1929).

been variously characterized as "affinity and rates," "point of equilibrium and degree of mobility," "extent and speed." The terminology is relatively unimportant, but the realization of a fundamental difference between the two groups of phenomena is of primary significance. Comparisons of the former type are limited to reversible reactions which under the conditions of study result in reaction mixtures containing calculable or measurable quantities of all the reactants. Such comparisons have been made, for example, for the strength of acids and of bases, the ester and acetal reactions, the dissociation of the hexasubstituted ethanes, the enolization of diketones and keto esters, the addition of hydrocyanic acid to aldehydes, the isomerization of unsaturated compounds, the rearrangement of halides, and the reduction of quinones.

The rate aspect of the problem of the relationship of constitution to chemical reactivity logically is divisible further into three sections because of the differences in the operations which must be resorted to in making the comparisons. In the first type of experimentation (B_1), rates are measured under *identical* conditions for the members of a group of compounds. In the second type of experimentation (B_2), the *severity* of the conditions necessary for bringing about a given transformation is determined for the compounds to be compared. In the third type of experimentation (B_3), the *relative rates* of simultaneous or *competitive* reactions are determined (for each of the compounds to be compared) under a standard set of conditions; actually the *amounts* of the products obtained from each compound are usually determined and compared with each other or with the amount of the original compound which underwent reaction.

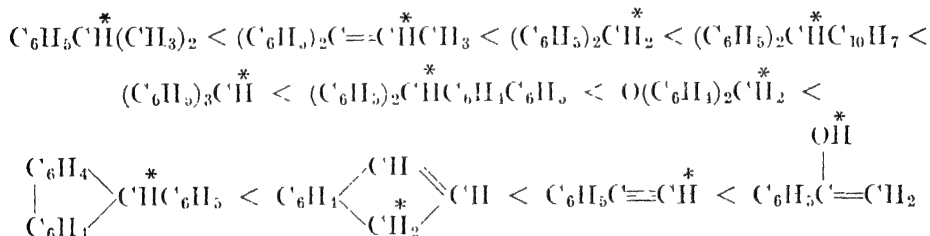
Comparisons of the relative chemical reactivity of substances based upon the rates of reaction might be carried out on any reaction, irrespective of whether it were reversible or irreversible, and, in fact, many such comparisons have been made. The illustrations of such comparisons given below are selected because of the care and completeness evidenced in the study, and perhaps because the author of this chapter was particularly interested in the results. Many equally meritorious pieces of work have been omitted because of the lack of space.

Strength of Acids and Bases. The most extensive comparisons with respect to the relation of structure of organic compounds to their chemical behavior in a reversible reaction have been those which were concerned with the strength of organic acids and bases.

The resulting data are so voluminous that no attempt will be made to present them here. However, the range in the strength of organic acids is much greater than would be indicated by the measurements

made in water solutions, on which most computations are based. Conant² has pointed out that the typical aliphatic carboxylic acid is perhaps 10^{20} as strong an acid as triphenylmethane yet acetamide in acetic acid is 10^6 as strong as acetic acid in water solution.

Conant and Wheland³ made a comparison of very weak acids by a novel method (p. 533) which took advantage of the partition of Na^+ or K^+ between the acid radicals, i.e., $\text{RH} + \text{R}'\text{K} \rightleftharpoons \text{RK} + \text{R}'\text{H}$. If a given R gives up hydrogen to R' then R is more acidic, i.e., negative, than R'. The exchange was carried out in ether between selected pairs of compounds from a group of eleven weak acids. Whether an exchange had taken place between a given pair of compounds was determined by the color changes in the ether solution or by carbonating the metallic compound after an opportunity for exchange had been allowed. The carboxylic acid so formed could then be isolated and characterized. As a result of these comparisons Conant and Wheland concluded that the order of increasing acidity of the compounds studied was as follows, the acidic hydrogen being starred:



Equilibria in Reaction of Hydrocyanic Acid with Aldehydes and Ketones. Lapworth and Manske⁴ determined the concentrations of hydrogen cyanide at equilibrium in the formation of cyanohydrins from aldehydes and ketones (p. 646), i.e., $>\text{C}=\text{O} + \text{HCN} \rightleftharpoons >\text{C}(\text{OH})\text{CN}$. A consideration of the procedure which they followed and of the precautions which they took is instructive. The reaction was carried out at 20° in alcohol (96 per cent $\text{C}_2\text{H}_5\text{OH}$, 4 per cent H_2O) in the presence of tripropylamine as a catalyst. Nitric acid was added to neutralize the catalyst after the completion of the reaction and before the uncombined hydrogen cyanide was estimated by addition of a standard solution of silver nitrate. The soluble silver was then estimated by titration. The quantity of catalyst (0.14 millimole) was small in proportion to the quantity of reactants (approximately 10 millimoles), thus insuring that even though the catalyst combined with one of the reactants the effective concentrations at equilibrium would be but little modified. It was

² Conant, *Ind. Eng. Chem.*, **24**, 466 (1932).

³ Conant and Wheland, *J. Am. Chem. Soc.*, **54**, 1212 (1932).

⁴ Lapworth and co-workers, *J. Chem. Soc.*, 2533 (1928); 1976 (1930).

ascertained that variations in the concentration of the catalyst did not affect the concentration of cyanide at equilibrium. That a true equilibrium had been attained was shown (a) by the fact that the same concentration of cyanide was found after 0.5 hour as after a day, and (b) by the fact that the value of the equilibrium "constant" was independent of the concentrations of the reactants.

Lapworth and Manske note that "It is evident that errors arising out of inaccurate measurements of the concentrations entering into the formula for the equilibrium constant are proportionately greatest when any of the three concentrations becomes very small, and this tends to be the case if the cyanohydrin has either a very low or a very high dissociation constant, the former being particularly unfavorable for accuracy. These considerations were always kept in mind while deciding the best ranges of concentration and proportions of constituents to be taken in the series of measurements made with each aldehyde and ketone examined."

It may be of interest to note in connection with the tabulation of results that an aldehyde or ketone having a value for K less than 0.1 (10 as tabulated) has a per cent conversion to the cyanohydrin of greater than 90 per cent when equimolecular amounts of carbonyl compound and hydrogen cyanide are allowed to react. The per cent conversion to

TABLE I
EFFECT OF SUBSTITUENTS ON THE EXTENT OF THE
REACTION OF HYDROGEN CYANIDE WITH DERIVATIVES
OF BENZALDEHYDE

| Substituent | $K \times 10^2$ | ΔF (kcal.) |
|-----------------------------|-----------------|--------------------|
| None (99%) | 0.47 | -3.1 |
| <i>o</i> -Nitro | 0.07 | -4.2 |
| <i>m</i> -Nitro | 0.27 | -3.4 |
| <i>p</i> -Nitro | 1.81 | -2.3 |
| <i>o</i> -Chloro | 0.10 | -4.0 |
| <i>m</i> -Chloro | 0.25 | -3.5 |
| <i>p</i> -Chloro | 0.49 | -3.1 |
| <i>o</i> -Methoxy | 0.26 | -3.5 |
| <i>m</i> -Methoxy | 0.43 | -3.2 |
| <i>p</i> -Methoxy (97%) | 3.12 | -2.0 |
| <i>o</i> -Hydroxy | 1.67 | -2.4 |
| <i>m</i> -Hydroxy | 0.48 | -3.1 |
| <i>p</i> -Hydroxy | 7.66 | -1.5 |
| <i>m</i> -Methyl | 0.60 | -3.0 |
| <i>p</i> -Methyl | 1.03 | -2.7 |
| 2-Me-4-MeO | 2.00 | -2.3 |
| 3-Me-4-MeO | 3.82 | -1.9 |
| <i>p</i> -Di-Me-amino (71%) | 39.00 | -0.5 |

TABLE II

EFFECT OF SUBSTITUENTS IN KETONES ON THE EXTENT
OF THE REACTION OF THE KETONE WITH HCN

| R CH ₃ COR | <i>K</i> × 10 ² | Δ <i>F</i> (kcal.) |
|--------------------------------------|----------------------------|--------------------|
| Methyl (97%) | 3.05 | -2.0 |
| Ethyl | 2.65 | -2.1 |
| <i>n</i> -Propyl | 3.55 | -1.9 |
| <i>n</i> -Butyl | 3.20 | -2.0 |
| Isopropyl | 1.55 | -2.4 |
| <i>tert.</i> -Butyl | 3.10 | -2.0 |
| Benzyl | 2.15 | -2.2 |
| β-Phenylethyl | 3.50 | -2.0 |
| γ-Phenylpropyl | 3.60 | -1.9 |
| C ₆ H ₅ COR | | |
| Methyl (46%) | 130 | +0.2 |
| Ethyl | 60 | -0.3 |
| <i>n</i> -Propyl (55%) | 90 | -0.05 |
| <i>n</i> -Butyl | 115 | +0.1 |
| <i>n</i> -Amyl | 130 | +0.2 |
| <i>n</i> -Hexyl | 115 | +0.2 |
| Isopropyl | 25 | -0.8 |
| Isobutyl | 155 | +0.3 |
| Isoamyl | 155 | +0.3 |
| Isohexyl | 125 | +0.1 |
| <i>tert.</i> -Butyl (91%) | 9 | -1.4 |
| Cyclohexyl | 40 | -0.6 |
| Phenyl | No reaction | |
| <i>Cyclic Ketones</i> | | |
| Cyclopentanone | 1.49 | -2.4 |
| Cyclohexanone | 0.09 | -4.1 |
| 2-Methylcyclohexanone | 0.06 | -4.3 |
| 3-Methylcyclohexanone | 0.30 | -3.4 |
| 4-Methylcyclohexanone | 0.13 | -3.9 |
| Cycloheptanone | 7.96 | -1.5 |
| Menthone | 6.54 | -1.6 |
| 3-Me-2- <i>iso</i> -Pr-cyclohexanone | | |
| α-Hydrindone | 610.0 | +1.1 |
| α-Ketotetrahydronaphthalene | 806.0 | +1.0 |
| Fluorenone | 146 | +0.2 |
| Camphor | No appreciable reaction | |
| Anthrone | No appreciable reaction | |
| Xanthone | No appreciable reaction | |

cyanohydrin of several carbonyl compounds with an equimolecular amount of hydrogen cyanide has been indicated in parentheses in the tables. The quantity K is the dissociation constant of the cyanohydrin into carbonyl compound and hydrocyanic acid; therefore, the higher the value of K the less the extent of the synthetic reaction.

A consideration of the data on the derivatives of benzaldehyde indicates that the substitution of a nitro, chloro, or methoxy group in the *ortho*-position to the aldehyde group increases the stability of the cyanohydrin as compared with benzaldehyde. The nitro, chloro, methoxy, hydroxy, and methyl groups have little or no influence in the *meta*-position; in the *para*-position all (except chloro) exert a markedly negative influence upon the stability of the addition product. The dimethyl-amino group in the *para*-position greatly decreases the stability of the cyanohydrins.

The data on the methyl ketones indicate that with the exception of the isopropyl group there is relatively little difference between methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, benzyl, phenylethyl, or phenyl-propyl. The affinity of these ketones for the addition of hydrogen cyanide is markedly lower than in the case of acetaldehyde and benzaldehyde. The phenyl ketones show a very low affinity for the addition of hydrogen cyanide, the ultimate effect being noted with diphenyl ketone which did not add hydrogen cyanide to an appreciable extent. The most striking fact brought out by these data on the phenyl ketones is that phenyl isopropyl ketone and phenyl *tert*-butyl ketone have the highest affinity for addition of hydrogen cyanide of any of the ketones studied. This is surprising because the secondary and tertiary alkyl radicals are in several reactions more like the aryl radicals than are the primary alkyl groups.

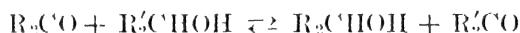
The data on the cyclic ketones apparently show that the cyclopentane ring increases affinity for hydrogen cyanide addition as contrasted with the corresponding open-chain ketone, while the cyclohexane ring materially increases further the tendency for addition of hydrogen cyanide. The seven-membered ring in cycloheptanone shows a low stability of the cyanohydrin while the other cyclic ketones studied show a very much lower affinity for addition of hydrogen cyanide than would saturated open-chain compounds.

Oxidation Potentials. The relative strengths as oxidizing agents of many quinones have been determined. The strength of a quinone as an oxidizing agent is usually expressed in volts with reference to the potential of the normal hydrogen electrode. The larger the value of the "oxidation" or "oxidation-reduction" potential of a quinone the more powerful is the quinone as an oxidizing agent. The reduction of a quinone to a hydroquinone is a strictly reversible process, and an

aqueous solution containing appreciable quantities of the two substances and a fixed hydrogen-ion concentration establishes a definite and accurately determinable potential at a platinum electrode. The values for typical quinones are: diphenoquinone 0.95, *p*-benzoquinone 0.71, 1,4-naphthoquinone 0.48, and 9,10-anthraquinone 0.15.

These four quinones differ very greatly from one another as oxidizing agents. For example, if equimolecular amounts of *p*-benzoquinone and 1,4-dihydroxynaphthalene were allowed to react there would be at equilibrium only one molecule of *p*-benzoquinone for approximately 10,000 molecules of 1,4-naphthoquinone.

The simple ketones and aldehydes appear to be somewhat similar to 9,10-anthraquinone as oxidizing agents.⁵ Their oxidation potentials cannot be ascertained by direct measurement at a hydrogen-platinum electrode, but the values can be calculated from the concentration at equilibrium in such a system as



where R_2CO is anthraquinone, for example, and R'_2CO is the ketone whose oxidation potential is desired. The equilibrium may be established in the presence of aluminum *tert.*-butoxide at 60 to 80°. By this method, the oxidation potential of benzaldehyde was found to be 0.20, cyclohexanone 0.19, acetone 0.16, and camphor 0.11 volt.

Heats of Hydrogenation. The relative reactivity of a series of compounds from the thermodynamical standpoint may be measured by means of the concentrations at equilibrium, as illustrated above for the addition of hydrogen cyanide, or by the determination of the potential set up at an electrode as in the case of the quinones. Another method of measurement depends upon a knowledge of the heats of reaction coupled with the use of the heat capacities of a series of compounds and the third law of thermodynamics.

One of the most precise and significant studies in relative reactivity by the latter method is that of Kistiakowsky and his associates.⁶ They measured directly the heats of hydrogenation of many compounds by carrying out the reaction catalytically in a calorimeter. The following comparisons are stated in terms of $-\Delta H$ at 355° K in kilogram calories. The values for ethylene, butene-1, and butene-2 are 32.6, 30.3, and 28.0, respectively, thus indicating the decrease in $-\Delta H$ with increase in substitution. A double bond in conjugation also decreases the value of $-\Delta H$. For example, the hydrogenation of one double bond in butadiene-1,3 gave a value of 26.7, while the value for butene-1 is 30.3

⁵ Baker and Adkins, *J. Am. Chem. Soc.*, **62**, 3305 (1940).

⁶ Kistiakowsky *et al.*, *ibid.*, **61**, 1868 (1939).

The most striking observation was that the value of $-\Delta H$ for the addition of one mole of hydrogen to benzene was $+5.6$. That is to say, the saturation of the first double bond in benzene is an endothermic reaction. The value of $-\Delta H$ for the second step in the hydrogenation of benzene is -26.7 , while the third step gives a value of -28.6 .

The data given above are intended merely for illustrative purposes since the original papers (1935 to 1939) are so valuable that they should be read by anyone interested in the relation of structure to the reactivity of the carbon-to-carbon double bond.

Equilibria in Enolization. Conant and Thompson⁷ have augmented in a very significant way our knowledge of the relationship of structure and the extent of enolization of β -keto esters and β -diketones. They "measured directly the equilibrium between a keto and an enol isomer in the gaseous phase (at low pressures), and thus obtained the free energy referred to the gaseous state ($\Delta F^\circ = -RT \ln K$).

"Since the interconversion of the two isomeric forms does not proceed directly in the gaseous phase, it was necessary to use the liquid phase as a go-between, as it were. This was accomplished by keeping an equilibrium mixture of the keto and enol forms at a given temperature and measuring the composition of the vapor in equilibrium with this mixture. Chemical and physical equilibrium conditions were assured by introducing a small amount of solid barium hydroxide as a catalyst and agitating the liquid sufficiently to keep renewing the surface in contact with the gas phase. The composition of the gas phase was determined by withdrawing it at very low pressure (without condensation) to a non-catalytic receiver at -80°C . where it was condensed without isomerization. It was then analyzed by the usual bromine titration method. The results are summarized in Table III.

"A study of the data shows that the regularities in the free energy of enolization referred to the gaseous phase are for the most part lacking when the liquid-phase value of K is employed for calculating ΔF . Thus, the large difference between acetoacetic ester and its alkyl derivatives (including benzyl) is masked by the disturbing solvent effects which here are of the order of 1 kcal. In the series of alkyl derivatives themselves, the gaseous-phase results show the essential similarity of the ethyl, *n*-propyl, and *n*-butyl compounds ($\Delta F^\circ = 1.2 \pm 0.1$ kcal.), and their definite but slight difference from the isopropyl derivative ($\Delta F^\circ = 1.6$ kcal.). It is interesting that the free energy of enolization, as determined with a dilute hexane solution, parallels the gaseous result closely. If further investigation shows that this is true for a large variety of substances, it would be a matter of some practical as well as theoretical

⁷ Conant and Thompson, *ibid.*, **54**, 4044 (1932).

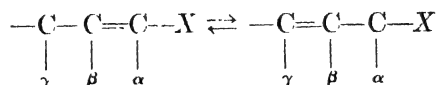
TABLE III
EXTENT OF ENOLIZATION
(Conant and Thompson)

| Substance | Gaseous State | | Pure Liquid | | In C ₆ H ₁₄ (0.1 M) | |
|---|---------------|------------|-------------|------------|---|------------|
| | % Enol | ΔF | % Enol | ΔF | % Enol | ΔF |
| CH ₃ COCH ₂ CO ₂ CH ₃ | 54 | -0.1 | 6 | 1.6 | | |
| CH ₃ COCH ₂ CO ₂ C ₂ H ₅ | 46 | 0.1 | 8 | 1.5 | 49 | 0.0 |
| CH ₃ COCH(CH ₃)CO ₂ C ₂ H ₅ . . | 14 | 1.1 | 4 | 1.9 | 11 | 1.1 |
| CH ₃ COCH(C ₂ H ₅)CO ₂ C ₂ H ₅ . | 10 | 1.3 | 3 | 2.1 | 14 | 1.1 |
| CH ₃ COCH(<i>n</i> -C ₃ H ₇)CO ₂ C ₂ H ₅ . | 13 | 1.1 | 7 | 1.5 | 14 | 1.1 |
| CH ₃ COCH(<i>iso</i> -C ₃ H ₇)CO ₂ C ₂ H ₅ . | 6 | 1.6 | 5 | 1.8 | 6 | 1.6 |
| CH ₃ COCH(<i>n</i> -C ₄ H ₉)CO ₂ C ₂ H ₅ . | 14 | 1.1 | 6 | 1.6 | 10 | 1.3 |
| CH ₃ COCH(<i>sec</i> -C ₄ H ₉)CO ₂ C ₂ H ₅ . | 9 | 1.4 | 8 | 1.4 | 9 | 1.3 |
| CH ₃ COCH(C ₆ H ₅)CO ₂ C ₂ H ₅ . | 80 | -0.8 | 30 | 0.5 | 67 | -0.4 |
| CH ₃ COCH(CH ₂ C ₆ H ₅)CO ₂ C ₂ H ₅ . | 12 | 1.2 | 5 | 1.8 | 12 | 1.2 |
| CH ₃ COCH ₂ COCH ₃ | 92 | -1.3 | 78 | -0.7 | 92 | -1.3 |
| CH ₃ COCH(CH ₃)COCH ₃ | 44 | 0.1 | 30 | 0.5 | 59 | -0.2 |
| CH ₃ COCH(C ₂ H ₅)COCH ₃ | 35 | 0.3 | 26 | 0.6 | 26 | 0.6 |
| CH ₃ COCH(CH ₂ C ₆ H ₅)COCH ₃ . . | 70 | -0.5 | 61 | -0.25 | 68 | -0.5 |
| CH(CO ₂ CH ₃) ₃ | 12 | 1.2 | 1 | 2.6 | | |
| C ₆ H ₅ COCH ₂ COCH ₃ | .. | .. | 99 * | .. | | |
| C ₆ H ₅ COCH(CH ₃)COCH ₃ | .. | .. | 6 * | .. | | |
| C ₆ H ₅ COCH ₂ COC ₆ H ₅ | .. | .. | 100 * | .. | | |
| C ₆ H ₅ COCH(CH ₃)COC ₆ H ₅ . . . | .. | .. | 0 * | .. | | |

* These values are from other sources.

importance, as there are a number of compounds which cannot be well studied by the gaseous-phase method. As those familiar with Kurt Meyer's work know, hexane is the solvent which most favors enolization. One may suppose that in this solvent we are most closely approaching the gas condition, as the mutual attractions of the keto and enol forms are diminished by dilution, and the saturated hydrocarbon has but slight molecular attractive forces."

Equilibria and Rates in Three Carbon Tautomerism. Among the most important and interesting studies on chemical reactivity are those having to do with the relationship of structure to the rate and extent of reaction in three carbon tautomerism (p. 1018):



R. P. Linstead has been so kind as to summarize in Table IV some of

TABLE IV
MOBILITY AND EQUILIBRIA IN THREE CARBON TAUTOMERISM OF CERTAIN ACIDS
CYANIDES, AND ESTERS
(Compiled by R. P. Linstead)

| Name of α,β -Compound | Substituents | | | | Equilibrium %, α,β - Compl. | Mobil- ity or Rate | Observers |
|--|--------------|---------|----------|-----------|--|--------------------------|--|
| | α | β | γ | γ' | | | |
| Acids ($X = \text{CO}_2\text{H}$) | | | | | | | |
| Crotonic | H | H | H | H | 98 | v. high | L. and Noble ⁸ |
| <i>n</i> -Pentenoic | H | H | Me | H | 68 | 9.8 | L. and Noble |
| <i>n</i> -Hexenoic | H | H | Et | H | 74 | 6.0 | L. and Noble |
| α -Methylpentenoic | Me | H | Me | H | 81 | 7.0 | Goldberg and L. ⁹ |
| α -Methylhexenoic | Me | H | Et | H | 89 | 18.8 | Kon, L., and Mac- lennan ¹⁰ |
| β -Methylpentenoic | H | Me | Me | H | 38 | 0.69 | Kon, L., and Wright ¹¹ |
| γ -Methylpentenoic | H | H | Me | Me | 22 | 1.5 | L. ¹² |
| β -Ethylpentenoic | H | Et | Me | H | 21 | 0.64 | Kon, Leton, Parsons, and L. ¹³ |
| γ -Ethylpentenoic | H | H | Me | Et | 22 | 3.1 | L. and Mann ¹⁴ |
| α,β -Dimethylpentenoic | Me | Me | Me | H | 72 | 0.12 | Kon, L., and Mac- lennan ¹⁰ |
| α -Methyl- β -ethylpen- tenoic | Me | Et | Me | H | 50 | 0.0058 | Kon, Leton, L., and Parsons ¹³ |
| Cyanides ($X = \text{CN}$) | | | | | | | |
| Butenoic | H | H | H | H | ca 98 | v. high | Letch and L. ¹⁵ |
| <i>n</i> -Hexenoic | H | H | Et | H | 86 | 930 | Letch and L. |
| β -Methylpentenoic | H | Me | Me | H | ca 99 | v. high | Kandiah and L. ¹⁶ |
| γ -Methylpentenoic | H | H | Me | Me | 21 | 170 | Letch and L. ¹⁵ |
| Ethyl Esters ($X = \text{CO}_2\text{Et}$) | | | | | | | |
| <i>n</i> -Hexenoic | H | H | Et | H | ca 92 | 153 | Kon, L., and Mac- lennan ¹⁰ |
| α -Methylhexenoic | Me | H | Et | H | 95 | 151 | Kon, L., and Mac- lennan |
| β -Methylpentenoic | H | Me | Me | H | 75 | 26 | Kon, L., and Mac- lennan |
| γ -Methylpentenoic | H | H | Me | Me | ca 10 | high | L. ¹⁷ |
| α,β -Dimethylpentenoic | Me | Me | Me | H | 91.5 | 2 | Kon, L., and Mac- lennan ¹⁰ |

⁸ Linstead and Noble, *J. Chem. Soc.*, 614 (1934).

⁹ Goldberg and Linstead, *ibid.*, 2343 (1928).

¹⁰ Kon, Linstead, and Maclellan, *ibid.*, 2452 (1932).

¹¹ Kon, Linstead, and Wright, *ibid.*, 599 (1934).

¹² Linstead, *ibid.*, 1603 (1930).

¹³ Kon, Leton, Linstead, and Parsons, *ibid.*, 1411 (1931).

¹⁴ Linstead and Mann, *ibid.*, 2064 (1930).

¹⁵ Letch and Linstead, *ibid.*, 443 (1932).

¹⁶ Kandiah and Linstead, *ibid.*, 2139 (1929).

¹⁷ Linstead, *ibid.*, 2498 (1929).

the more significant numerical results of these studies which have to do with the behavior of acyclic compounds where X is COO^- , CN , or CO_2Et .

The acids were equilibrated in aqueous solution in the presence of excess alkali at 100° .¹⁸ The cyanides and esters were equilibrated in an alcoholic solution using sodium ethoxide as a catalyst at 25° .¹⁹ The analytical method was that described by Linstead and May²⁰ and depends upon the difference in the ease of addition of iodine to alkene linkages in the β,γ - as contrasted with those in the α,β -position.

The data in the table make it clear that at equilibrium unsubstituted acids exist almost entirely in the α,β -form. One γ -substituent is essential to give some β,γ stability while a second γ -substituent makes the β,γ -unsaturated compound the major component of the equilibrium mixture. β -Substitution favors the β,γ -phase but not so powerfully as does γ -substitution. The general effect of the position of substituents upon the proportion of the tautomers is the same in the three types of compounds investigated. However, in certain cyclic acids the β,γ -form is favored, e.g., 85 per cent β,γ for cyclopentylideneacetic acid, 88 per cent for cyclohexylideneacetic acid, and 67 per cent for cycloheptylideneacetic acid.

β - and γ -substituents have much the same effect in ketones as in acids and esters, but an α -alkyl group causes not only a great diminution of mobility but also a pronounced shift in equilibrium towards the β,γ -form. The cyclic ketones show remarkable differences; for example, Kon observed 77 per cent α,β for cyclopentylideneacetone, 23 per cent α,β for cyclohexylideneacetone, and 40 per cent α,β for cycloheptylideneacetone.²¹

There is little or no correlation between the rate of tautomerization (mobility) and the extent of the reaction. Alkylation on the β -carbon decreases the mobility, while α -alkylation produces an enormous slowing in an already heavily alkylated system but not otherwise except in the ketones. It should be noted that certain β -alkylated substances show an exceptionally high mobility in acid but not in alkaline media. This is attributed by Linstead to the readily reversible addition of acid anions to a carbon atom of the type $\text{R}_2\text{C}=\text{C}$.

Unsaturated acids tautomerize in the absence of added reagents at temperatures near their boiling points¹² by what appears to be an intramolecular reaction.⁸ Special precautions must be taken in order to insure that a preparation of an unsaturated compound is homogeneous

¹⁸ Linstead, *J. Chem. Soc.*, 2579 (1927).

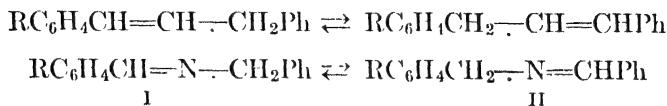
¹⁹ Kon and Linstead, *ibid.*, 1269 (1929).

²⁰ Linstead and May, *ibid.*, 2565 (1927).

²¹ Kon, *ibid.*, 1616 (1930); *Ann. Repts. Chem. Soc. (London)*, **27**, 138 (1930).

and not a mixture of tautomers. During the period of equilibration it is necessary to guard against the formation of lactones, ethoxy esters, and other products.

Shoppee²² has studied the effect of substituents in the diarylpropene and diarylmethyleneazomethine series.



With respect to the mobility of these systems he "has shown that the variants R in either the *m*- or *p*-position fall into the serial order $\text{Me}_2\text{N} < \text{Me} < \text{MeO} < \text{I} < \text{Br} < \text{Cl} < \text{NO}_2$, which is also the order of the dipole moments (Chapter 23) of the compounds $\text{R}-\text{C}_6\text{H}_4-$." The mobilities of the six halides were similar, 6.8 (*m*) to 10.7 (*p*), the methoxyls 0.6 (*m*) to 2.5 (*p*), the methyl 0.3 (*m*) to 1.1 (*p*), and the dimethylamino 0.05 (*m*) to 0.6 (*p*) for methyleneazomethine series. With respect to the proportion of the isomers at equilibrium, Shoppee found that the percentage of the I isomer for the latter series was for various substituents as follows: NO_2 , 68 per cent; Me_2N , 63 per cent; Me, 60 per cent; MeO, 55 per cent; I, 42 per cent; Br, 36 per cent; Cl, 35 per cent.

Equilibria and Rates in Esterification and Alcoholysis. The relation of the structure of the alcohol and the acid to the rate and extent of esterification has been extensively studied. The comparison of acids with respect to their relative rates of reaction with a given alcohol is not a simple one, since the rate of the esterification reaction is a function of the concentration of the catalyst and the catalyst is the acid or one of its dissociation products, the solvated proton. In other words, when the rate of esterification of two acids is measured the resultant rate constant is a function not only of the rate of reaction of the acid but also of the activity of the acid as a catalyst for its own esterification. Since the rate of esterification, over certain ranges of concentration, is proportional to the hydrogen-ion concentration, it is possible to calculate the rate of reaction to a standard hydrogen-ion concentration.

The data given in Tables V and VI are from the papers of Menshutkin²³ and indicate the relative rates of reaction of various alcohols and acids without added catalyst. The retarding effect of branching of the carbon chain shown by trimethyl- and dimethylethylacetic acids is even more marked in the 2,6-disubstituted benzoic acids, which do not react with alcohols under any known conditions.

²² Shoppee, *J. Chem. Soc.*, 1117 (1933).

²³ Menshutkin, *Ann. chim. phys.*, [5] **30**, 81 (1883).

TABLE V

AMOUNT OF ESTERIFICATION OF VARIOUS ALCOHOLS BY ACETIC
ACID IN 1 HOUR AT 155°

| Primary | % | Secondary | % | Tertiary * | % |
|-----------------|------|-------------------------|------|---------------------------|-----|
| Methyl | 55.6 | Dimethylcarbinol | 26.5 | Trimethylcarbinol | 1.4 |
| Ethyl | 46.9 | Methylethylcarbinol | 22.6 | Dimethylethylcarbinol | 0.8 |
| Propyl | 46.9 | Methylhexylcarbinol | 21.2 | Methyldiethylcarbinol | 1.0 |
| <i>n</i> -Butyl | 46.8 | Methylisopropylcarbinol | 18.9 | Dimethylpropylcarbinol | 2.1 |
| <i>n</i> -Octyl | 46.6 | Diethylcarbinol | 16.9 | Dimethylisopropylcarbinol | 0.9 |

* Dehydration also takes place.

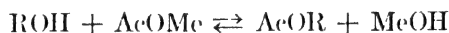
TABLE VI

AMOUNT OF ESTERIFICATION OF VARIOUS ACIDS BY ISOBUTYL ALCOHOL
IN 1 HOUR AT 155°

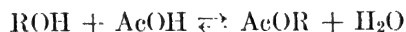
| | | | | | |
|-----------|------|------------|------|-------------------------|------|
| Formic | 61.7 | Butyric | 33.3 | α -Methylbutyric | 21.5 |
| Acetic | 44.4 | Caprylic | 30.9 | Trimethylacetic | 8.3 |
| Propionic | 41.2 | Isobutyric | 29.0 | Dimethylethylacetic | 3.5 |

The extent of the reaction was 65-70 per cent for the primary alcohols, 50-60 per cent for secondary alcohols, and less than 5 per cent for tertiary alcohols. The extent of reaction of an alcohol and an acid in a homogeneous system is not modified by the catalyst or, except to a slight extent, by the temperature at which the reaction is studied. However, the difference between the extent of reaction of ethyl alcohol and acetic acid in the liquid phase (67 per cent) and over silica gel is striking. Reid gives for the latter the following figures: 150°, 85 per cent; 200°, 83 per cent; 250°, 78 per cent; 300°, 75 per cent.

The equilibrium constant for various alkyl groups (R) has been calculated for the alcoholysis reaction,



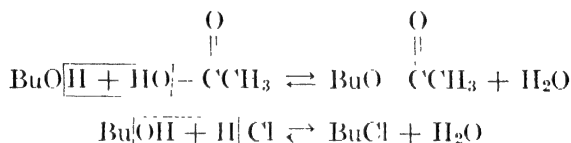
and the relative values found to be similar to those for the esterification reaction,



The values of the equilibrium constant for various alkyl groups in alcoholysis are as follows: 2-ethylhexyl, 1.02; methyl, 1.00; *n*-amyl, 0.95; *n*-heptyl, 0.77; *n*-dodecyl, 0.71; 3-phenylpropyl, 0.69; ethyl, 0.66; *sec*-amyl, 0.64; *n*-butyl, 0.64; *n*-propyl, 0.62; *sec*-heptyl, 0.5; 2-octyl, 0.46; isobutyl, 0.44; 2-phenylethyl, 0.42; allyl, 0.38; benzyl, 0.35; isopropyl, 0.30; cyclohexyl, 0.32; and *sec*-butyl, 0.28. The corresponding value for hydrogen (0.19) is less than for any of these alkyl groups.²⁴

²⁴ Fehlandt and Adkins, *J. Am. Chem. Soc.*, **57**, 193 (1935). Hatch and Adkins, *ibid.* **59**, 1694 (1937).

There is a very great difference between primary, secondary, and tertiary alcohols and the halogen acids on the one hand and the carboxylic acids on the other. The order of increasing rate of reaction of the alcohols with the halogen acids is: primary < secondary < tertiary, an order which is the reverse of that observed for acetic acid, for example. This is illustrated by the well-known fact that hydrochloric acid does not react at a measurable rate with *n*-butyl alcohol at room temperatures, yet *tert*-butyl chloride is formed almost instantly and in high yield from *tert*-butyl alcohol under the same conditions. Acetic acid reacts more slowly and to a much less extent with *tert*-butyl than with *n*-butyl alcohol. These facts may be rationalized by assuming that with acetic acid the hydroxyl group entering into the formation of water comes from the acid while with hydrochloric it must come from the alcohol. There is reason for believing that the hydrogen of the hydroxyl of a primary alcohol is more rapidly replaced than that of a tertiary alcohol, while the hydroxyl of a tertiary is more rapidly replaced than that of a primary alcohol.



Equilibria and Rates in Formation of Acetals. The concentration of the aldehyde at equilibrium has been determined in the formation of more than a hundred acetals.²⁵ A selection from the data so obtained with respect to acetaldehyde and tetrahydrofurfural is given in Table VII. If the behavior of ethyl, propyl, butyl, pentyl, and heptyl alcohols with acetaldehyde, propionaldehyde, butyraldehyde, or heptaldehyde is accepted as a standard then the per cent conversion of the straight-chain aldehyde with the straight-chain primary alcohols is 80 per cent for 1 mole of aldehyde to 5 moles of alcohol. Similarly, for 8 acetals formed from simple aldehydes and the secondary alcohols propanol-2, butanol-2, pentanol-2, and octanol-2, the average per cent conversion at equilibrium was 46 per cent, while two tertiary alcohols gave a conversion of about 20 per cent. The effect of various structures upon the extent of reaction is shown by the figures in Table VIII which indicate the divergence of the per cent conversion actually observed from the values which were noted as characteristic of the simpler aldehydes and alcohols.

The figures in the first column of Table VIII reveal the fact that substitution of methyl groups in acetaldehyde results in a greatly low-

²⁵ For leading references to work of Adkins, E. W. Adams, Hartung Street, Broderick Minne, and Dunbar, see *ibid.*, **56**, 442 (1934).

TABLE VII
EXTENT OF REACTION OF ALDEHYDES AND ALCOHOLS
(5 MOLES ALCOHOL TO 1 MOLE ALDEHYDE)

| Alcohol | Acetaldehyde | | Tetrahydrofurfural | |
|--------------------|--------------|------|--------------------|------|
| | % Conversion | K | % Conversion | K |
| 3-Phenylpropyl | 96 | 13.3 | 95 | 9.5 |
| <i>n</i> -Octyl | | | 95 | 9.5 |
| <i>n</i> -Dodecyl | | | 90 | 4.0 |
| <i>n</i> -Pentyl | 93 | 6.5 | 83 | 3.5 |
| 2-Phenylethyl | 92 | 5.4 | 89 | 3.5 |
| <i>n</i> -Heptyl | 92 | 5.4 | 95 | 9.5 |
| <i>n</i> -Butyl | 88 | 3.1 | 80 | 1.4 |
| Isobutyl | 88 | 3.1 | 78 | 1.2 |
| Methyl | 87 | 2.4 | 86 | 2.3 |
| Ethyl | 78 | 1.2 | 79 | 1.3 |
| 2-Iodoethyl | 78 | 1.2 | | |
| <i>n</i> -Propyl | 76 | 1.1 | 80 | 1.4 |
| 2-Chloroethyl | 76 | 1.1 | 76 | 1.1 |
| 2-Ethoxyethyl | 74 | 0.91 | 79 | 1.3 |
| Benzyl | 74 | 0.91 | 79 | 1.3 |
| Allyl | 73 | 0.84 | 72 | 0.77 |
| 2-Bromoethyl | 71 | 0.76 | | |
| Cyclohexylethanol | 76 | 0.26 | | |
| Cyclohexanol | 56 | 0.26 | 88 | 3.1 |
| Pentanol-2 | 53 | 0.23 | | |
| Butanol-2 | 46 | 0.13 | 65 | 0.47 |
| Octanol-2 | 46 | 0.13 | 90 | 4.0 |
| Propanol-2 | 39 | 0.10 | 49 | 0.17 |
| <i>tert</i> -Butyl | 23 | 0.02 | 38 | 0.07 |

TABLE VIII
COMPARISONS IN ACETAL FORMATION

| Aldehyde | Ethanol | Cyclohexyl- carbinol | Cyclo- hexanol | Propanol-2 | Octanol-2 |
|-------------------|---------|-------------------------|-------------------|------------|-----------|
| Acet- | -2 | -24 | +10 | -3 | 0 |
| Dimethylacet- | -9 | -38 | ... | -23 | ... |
| Trimethylacet- | -24 | -38 | -30 | -35 | -20 |
| Cyclopentyl- | -35 | -39 | -11 | -33 | +4 |
| Benz- | -41 | -45 | -23 | -32 | +3 |
| Hexahydrobenz- | -2 | +7 | +29 | -17 | +28 |
| Furfur- | -49 | | | -29 | -35 |
| Tetrahydrofurfur- | -1 | ... | +42 | +3 | +44 |

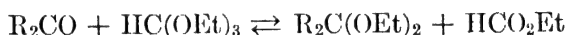
* The figures given in the table are obtained by subtracting 80 (primary alcohols) or 46 (secondary alcohols) from the percentage conversion to the acetal of 5 moles of alcohol and 1 mole of aldehyde.

ered per cent conversion to the acetal in the reaction with ethanol. The cyclopentyl radical had a similar effect, while the cyclohexyl group had no effect when attached to the aldehyde group. Unsaturation in the aldehyde as indicated by the differences between benzaldehyde and hexahydrobenzaldehyde, or furfural and tetrahydrofurfural, also greatly decreased the conversion to acetal. The same tendency was also noted with acrolein ($K = 0.17$), crotonaldehyde (0.011), and cinnamaldehyde (0.013), the effect being especially marked with the latter two which were lower than benzaldehyde (0.16).

If the behavior of the cyclic alcohols and cyclic aldehydes toward each other is noted it is seen that the relationships are quite far from being as consistent as in simpler aldehydes and alcohols. For example, cyclohexylcarbinol gives a much lower value for acetaldehyde than do other primary alcohols, while cyclohexanol gives a higher value than do the simpler secondary alcohols. Cyclohexanol and octanol-2 also give abnormally high values with the cyclic aldehydes.

The studies on the relation of the structure of the aldehyde and alcohol to the rate of the acetal reaction are much less comprehensive than those with respect to the extent of the reaction described above. The matter may be covered in a qualitative way by the statement that the unsaturated aldehydes, benzaldehyde, furfural, cinnamic aldehyde, and crotonic aldehyde react many times more rapidly than such saturated aldehydes as acetaldehyde, tetrahydrofurfural, and especially hexahydrobenzaldehyde.

The effect of structure upon the formation of acetals from ketones has also been studied on the basis of the reversible reaction,



The effect of branching of the carbon chain and of phenyl groups upon decreasing the tendency to form acetals is evident from the data in Table IX.²⁶

TABLE IX

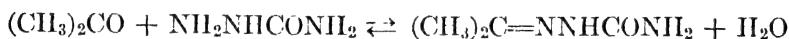
EXTENT OF ACETAL FORMATION IN REACTION OF 0.1 MOLE OF ORTHOFORMIC ESTER WITH 0.1 MOLE OF VARIOUS KETONES IN A SOLUTION MADE UP TO 50 ML. WITH ETHYL ALCOHOL

| Ketone | % Acetal | Ketone | % Acetal |
|-----------------------------|-------------|-------------------------------|-------------|
| Dimethyl | 95 | Methyl <i>tert.</i> -butyl | 50 |
| Methyl ethyl | 90 | Ethyl <i>tert.</i> -butyl | 36 |
| Methyl β -phenylethyl | 89 | Diphenyl | 34 |
| Methyl phenyl | 86 | <i>tert.</i> -Butyl isopropyl | 36 |
| Methyl neopentyl | 84 | Di- <i>tert.</i> -butyl | 17 |
| Di-isopropyl | 65 | | |

²⁶ Pfeiffer and Adkins, *ibid.*, **53**, 1043 (1931).

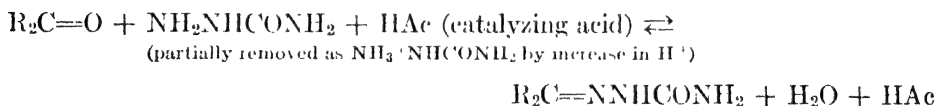
Equilibria and Rates in the Formation of Semicarbazones. The formation of semicarbazones has been quantitatively studied by Conant and Bartlett.²⁷ The exposition of this study made by Conant is so significant that it is quoted below.²

"This is a case where an equilibrium controls the rate but, in addition, acid catalysis is involved. The results illustrate the great importance to organic chemistry of the general theory of acid and basic catalysis developed by Brönsted and Lowry in the last few years. The general reaction may be illustrated by the reaction of acetone:



The reaction is reversible, and this fact must be taken into account, of course, in formulating the kinetic equations where the back reaction is appreciable.

"A study of the reaction rate in a variety of buffer solutions has shown that two opposing factors are at work. On the one hand, an increase in acidity of the solution beyond about $p\text{H} = 4.9$ decreases the amount of free semicarbazide by salt formation (the pK of $\text{NH}_3^+\text{NHCONH}_2$ is 3.66 at 25°C .) and thus diminishes the rate, since the reaction is between the free base and the carbonyl compound. On the other hand, this very reaction between the free base and the carbonyl compound is subject to acid catalysis, and its rate increases with the concentration of the acid:



In an ordinary set of buffer solutions covering a narrow range, increase of acidity is effected by increasing the concentration of free acid. Therefore, rate measurements in such buffers show a pronounced maximum." The data "might easily lead to the erroneous conclusion that the rate was controlled solely by the $p\text{H}$ value of the buffer. Measurements made at constant $p\text{H}$ but varying concentration of buffering materials, however, show that the rate is proportional to the concentration of catalyzing acid. The apparent regularity [of the relationship of rate of reaction and $p\text{H}$] is thus the result of an accidental conformity between $p\text{H}$ and acid concentration—a consequence of the usual way of making a series of buffers." This point is further illustrated by the fact that the relationship of $p\text{H}$ to rate of reaction is different with phosphate from that with acetate as a buffer.

²⁷ Conant and Bartlett, *ibid.*, **54**, 2881 (1932).

"In general, in cases of acid catalysis, the specific catalytic effect of the acid is greater, the stronger the acid. For this reason the most effective catalyst for semicarbazone formation would be an acid only slightly weaker than the semicarbazide ion, $\text{NH}_3^+\text{NHCONH}_2$. Such an acid is acetic (about 1 pK unit weaker); a large concentration of this acid can be introduced into the solution, and, by an appropriate increase in sodium acetate concentration, the pH value can be kept sufficiently high so that only a small portion of the semicarbazide is combined with the acid. To some extent these optimum conditions are approached when potassium acetate and semicarbazide hydrochloride are employed in the preparation of semicarbazones. It would probably be advantageous, however, to increase the concentration of the catalyst (acetic acid), at the same time keeping the pH high by the addition of acetate ion.

"It is evident that, in comparing the equilibria and the rates of semicarbazone formation with a variety of carbonyl compounds, the experiment should be performed in such a manner that a definite amount of catalyst is present in each case and that practically all the semicarbazide and condensation product should be present as the free base. A phosphate buffer of pH about 7 and a concentration of catalyst (H_2PO_4^-) of about 0.06 M meet these specifications. The results obtained under such conditions are summarized in Table X.

TABLE X

COMPARISON OF EQUILIBRIA AND RATES OF SEMICARBAZONE FORMATION OF KETONES AND ALDEHYDES

(At $25^\circ \pm 0.01^\circ\text{C}$. in 0.07 M Na_2HPO_4 + 0.03 M NaH_2PO_4)

| | $K \times 10^5$ Hydrolysis Constant of Semicarbazone | Velocity Constants of Semicarbazone Formation & Hydrolysis | |
|-----------------------|--|--|-------------------|
| | | k_2 | $k_1 \times 10^4$ |
| Acetaldehyde | 2.9 | 361 | 1040 |
| Benzaldehyde | 0.30 | 2.05 | 0.62 |
| Furfural | 0.76 | 0.73 | 0.55 |
| Trimethylacetaldehyde | 1.85 | 20 | 37 |
| Pyruvic acid | 0.51 | 7.37 | 3.8 |
| Acetone | 324 | 6.02 | 1800 |
| Cyclohexanone | 214 | 36 | 7600 |
| Pinacolone | 1260 | 0.068 | 66 |

"A consideration of Table X brings out a number of points of interest. In the first place, it is clear that there is no apparent relation between the speed of formation of the semicarbazone and its stability

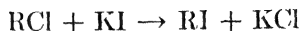
as measured by the hydrolysis constant, K . Considering first the relation between structure and rate of semicarbazone formation, acetaldehyde is found at the top of the list, with its trimethyl substitution product about a tenth as reactive, but some ten times more reactive than benzaldehyde or furfural. The latter is the least reactive of all the aldehydes and differs from acetaldehyde by nearly a thousandfold. Of the ketones, cyclohexanone is the most reactive (as would have been expected from previous work), and acetone and pyruvic acid are essentially equal and about a sixth as rapid in semicarbazone formation as the cyclic ketone. The large drop in reactivity caused by substitution of three methyl groups (0.068 for pinacolone compared with 6.0 for acetone) is in accord with a large variety of qualitative and quantitative facts of organic chemistry. A comparison of benzaldehyde, furfural, acetone, and trimethylacetaldehyde gives very little support to the idea that the rate of carbonyl reaction is determined solely by so-called steric effects. It would seem that the facts are much too complicated to be explained solely by such a simple hypothesis. However, if attention is confined to a particular limited class of compounds, such as the aldehydes, the concept of steric hindrance affords a plausible explanation of relation between rates and structure. The comparison of acetone, pinacolone, and acetaldehyde and its trimethyl derivative illustrates this.

"Turning now to the equilibrium constants, we find all the ketones (except pyruvic acid) falling into one class and the aldehydes into another. Within the ketone class the variation in the hydrolysis constant is only threefold, the most highly substituted ketone being the most completely hydrolyzed. The variation among the aldehydes is tenfold, but the difference between the least-hydrolyzed ketone semicarbazone (always excepting pyruvic acid) and the most-hydrolyzed aldehyde semicarbazone is a hundredfold. It would appear that the carbonyl compounds, as far as the energy relationships are concerned, show a rather simple relationship between structure and semicarbazone formation, the equilibrium constants being determined by the same sort of factors which determine the dissociation constants of acids. For convenience, these factors may be termed the 'polarity' or 'negativity' of the attached groups. Thus we may say that the more negative the atoms or groups X, Y in the compound, XC'OY , the less hydrolyzed is the semicarbazone. The contrast between aldehydes and ketones corresponds to the difference in strength of formic and the other aliphatic acids. The fact that pyruvic acid semicarbazone is even less hydrolyzed than that of acetaldehyde is in accord with the greater strength of oxalic acid ($pK = 2.8$) as compared with formic acid ($pK = 3.7$).

"Some of the conclusions summarized in Table X can be demonstrated by qualitative experiments which also serve to emphasize the difference between rates and equilibria in controlling organic reactions. The most striking of these experiments involves a comparison of cyclohexanone and furfural. The differences in rates of semicarbazone formation are in favor of the former by a factor of about fifty; the hydrolysis of the aldehyde semicarbazone is only one three-hundredth of that of the ketone, however. As a result, if one mole of semicarbazide and one mole each of cyclohexanone and furfural are allowed to react, practically the entire final product is furfural semicarbazone. Because of the differences in the rates of reaction, however, the initial product in such an experiment is almost wholly cyclohexanone semicarbazone. The effect of these differences in rate and equilibrium constants can be shown very simply by allowing semicarbazide to react with a mixture of cyclohexanone and furfural in alcoholic solution and isolating the semicarbazone after a few seconds and after a few hours. (Because of the solubility of cyclohexanone semicarbazone in water, it is necessary to precipitate the product by pouring a sample of the mixture into a saturated ammonium sulfate solution in which the cyclohexanone semicarbazone is almost insoluble.) In such an experiment, starting with 0.01 mole each of semicarbazide hydrochloride, furfural, and cyclohexanone, and 0.05 mole of potassium acetate in 50 per cent alcohol, a sample precipitated after 20 seconds yielded cyclohexanone semicarbazone, while after 2.5 hours a similar precipitate was found to be pure furfural semicarbazone.

"It is worth noting that, if one had attempted to draw conclusions about the relative reactivity of the two carbonyl compounds from one of the above experiments alone, the conclusions would have been diametrically opposite, depending on whether the product was isolated after a few seconds or after a few hours. This is an illustration of the difficulties of attempting to deduce generalizations in regard to the behavior of organic compounds from qualitative experiments when the nature of the reaction is not fully understood. There seems no escape from the conclusion that significant comparisons of quantitative measurements can be made only on the basis of a thorough knowledge of a reaction. This requires first a detailed study of the yields of all the products and later a physicochemical study of the factors which control the equilibrium and the rate. The amount of work involved in such studies and the complications already unearthed are welcome guarantees that there will be many problems to solve for a long time to come. We may rest confident, moreover, that the fascinating art of organic chemistry will yield only slowly to the devastating inroads of an exact science."

Rates of Reaction of Alkyl Chlorides and Metallic Iodides. Conant, Kirner, and Hussey²⁸ made a study of the relation of structure to the rate of reaction of some fifty halogen compounds with potassium iodide



The rates of the reaction in acetone were measured at various temperatures from -10° to 60° . They showed that there was no appreciable amount of a "side reaction" and that the relative rates of different alkyl halides were approximately independent of the temperature at which the comparison was made. This latter observation made it feasible to calculate the relative rates of reaction to a standard temperature (50°) even though the experimental results were obtained at the various temperatures at which the reactions proceeded at a measurable rate. The reaction was not reversible. The relative rates were independent of the concentration of the reactants, and independent of whether the metallic iodide was sodium, lithium, or potassium.

The reaction rate constant was calculated upon the basis of the usual bimolecular equation, but a better comparison of the rates of reaction is given as the result of a calculation in which the rate of reaction of *n*-butyl chloride is unity. Such a comparison is given in Table XI. It may be of interest to note that at 50° butyl chloride had reacted to the extent of 50 per cent after 36 hours, whereas only 15 hours was required at 60° . ω -Chloroacetophenone at 0° had reacted to the extent of 55 per cent after less than 1 minute. Allyl chloride at 25° had reacted to the extent of 51 per cent after 6.3 hours.

Many interesting and important comparisons and conclusions may be made upon the basis of the data given in the table, but it must suffice to point out only a few of these: The normal alkyl halides are very similar in their behavior towards potassium iodide. The secondary and tertiary alkyl halides are similar to each other but very much less reactive than the primary chlorides. Cyclohexyl chloride is almost as unreactive in this reaction as the aryl halides.

The structure $\text{C}=\text{C}-\text{C}-\text{Cl}$ as found in allyl or benzyl chloride results in enhanced reactivity of the halogen. The phenyl, carbonyl, carboethoxy, cyano, amido, methoxy, nitrophenyl, bromophenyl, and chlorophenyl groups showed a marked labilizing effect when attached to the carbon holding the chlorine.

Some of the more general conclusions are quoted from the original papers. "For purposes of expressing numerically the factors governing the behavior of organic substances as we deal with them in the labora-

²⁸ Conant, Kirner, and Hussey, *ibid.*, **46**, 232 (1924); **47**, 476, 488 (1925).

TABLE XI

RELATIVE REACTIVITIES OF CHLORIDES WITH POTASSIUM IODIDE

| Compound | Relative Reactivity | Compound | Relative Reactivity |
|--|---------------------|--|---------------------|
| <i>n</i> -C ₄ H ₉ Cl | 1 00 | C ₆ H ₅ COCH ₂ Cl | 105,000 |
| C ₂ H ₅ Cl | 1 94 | CH ₃ COCH ₂ Cl | 35,700 |
| <i>n</i> -C ₃ H ₇ Cl | 1 03 | NCCH ₂ Cl | 3,070 |
| <i>n</i> -C ₅ H ₁₁ Cl | 1 26 | C ₂ H ₅ O ₂ CCl ₂ Cl | 1,720 |
| <i>n</i> -C ₆ H ₁₃ Cl | 1 22 | CH ₃ OCH ₂ Cl | 918 |
| <i>n</i> -C ₇ H ₁₅ Cl | 1 20 | C ₆ H ₅ COCl | 700 |
| <i>n</i> -C ₈ H ₁₇ Cl | 1 32 | CH ₃ CO ₂ C ₂ H ₅ Cl | 270 |
| <i>n</i> -C ₁₂ H ₂₅ Cl | 1 00 | C ₆ H ₅ CO(C ₂ H ₅) ₃ Cl | 230 |
| <i>n</i> -C ₁₆ H ₃₃ Cl | 0 90 | H ₂ NCOC ₂ H ₅ Cl | 99 |
| <i>n</i> -C ₃₀ H ₆₁ Cl | 0 88 | CH ₂ =CHCH ₂ Cl | 79 |
| <i>iso</i> -C ₅ H ₁₁ Cl | 0 65 | C ₂ H ₅ O ₂ CCl | 26 |
| (CH ₃) ₂ CHCl | 0 015 | C ₆ H ₅ CH ₂ Cl | 195 |
| C ₂ H ₅ CHClCH ₃ | 0 022 | (C ₆ H ₅) ₃ CCl | 38,000 |
| <i>n</i> -C ₃ H ₇ CHClCH ₃ | 0 048 | (C ₂ H ₅ O ₂ C) ₂ CHCl | 60,200 |
| <i>n</i> -C ₁₁ H ₉ CHClCH ₃ | 0 075 | <i>o</i> -NO ₂ C ₆ H ₄ CH ₂ Cl | 1,800 |
| <i>n</i> -C ₆ H ₁₃ CHClCH ₃ | 0 026 | <i>m</i> -NO ₂ C ₆ H ₄ CH ₂ Cl | 780 |
| (CH ₃) ₃ CCl | 0 018 | <i>p</i> -NO ₂ C ₆ H ₄ CH ₂ Cl | 1,370 |
| <i>cyclo</i> -C ₆ H ₁₁ Cl | 0 0001 | 2,4-(NO ₂) ₂ C ₆ H ₃ CH ₂ Cl | 50,800 |
| C ₆ H ₅ (CH ₂) ₂ Cl | 0 91 | <i>o</i> -ClC ₆ H ₄ CH ₂ Cl | 718 |
| C ₆ H ₅ (CH ₂) ₃ Cl | 1 35 | <i>p</i> -ClC ₆ H ₄ CH ₂ Cl | 553 |
| C ₆ H ₅ (CH ₂) ₆ Cl | 1 07 | <i>o</i> -BrC ₆ H ₄ CH ₂ Cl | 77,300 |
| | | <i>p</i> -BrC ₆ H ₄ CH ₂ Cl | 48,100 |

tory, differences in reactivity of 25 or even 50 per cent are of relatively little importance. Variations of threefold, a hundredfold and a millionfold are the cause of the vagaries which make our present structural formulas so often unreliable in predicting reactions. From this point of view the results of all the previous studies of primary halides and the data here presented may be said to be in general agreement. In a great variety of reactions a methyl halide is 5 to 20 times more reactive than the ethyl compound which in turn is only about twice as reactive as the other primary straight-chain compounds that do not differ materially from one another, at least as high in the series as C₃₀H₆₁Cl. The forking of the chain diminishes the reactivity of primary compounds, which diminution in the case of amyl is about 100 per cent (our results are in agreement with those of two other investigators on this point).

"The discrepancies in regard to the comparison of primary and secondary halides are serious; they may be real differences, specific for each of the reagents employed, or they may be due to the fact that in certain instances some unsuspected reaction may be taking place with the secondary compounds which is absent from the primary series.

For example, any comparison of the action of alcoholates on primary and tertiary halides is meaningless because in the one case ethers are formed and in the second olefins. We have chosen the reaction with an inorganic iodide in absolute acetone because of the impossibility of many side reactions which may complicate the results with other reagents used in aqueous or alcoholic solution and because the reaction has been widely used for preparative purposes and is known to give excellent yields. We are, therefore, inclined to believe that our results showing that secondary and tertiary halides are only 0.65 to 0.01 as reactive as primary compounds represent a correct formulation of the behavior of these substances, at least in simple metathetical reactions. There is already some evidence that seems to indicate that the rate of hydrolysis (and perhaps alcoholysis) in neutral solution does not parallel the rate of our metathetical reaction. Thus, in the previous paper ω -chloroacetophenone was found to be by far the most reactive substance, and yet it can be recrystallized without appreciable loss from mixtures of water and alcohol; a similar drastic treatment of benzoyl chloride or ethyl chlorocarbonate would insure very considerable hydrolysis and yet their relative reactivity on our scale is about one one-hundredth that of chloroacetophenone. Possibly some similar direct action between the secondary halides and the alcohol used as a solvent may be the cause of the relatively high reactivity found by some workers for these compounds."

Rates of Reaction of Diphenylchloromethanes and Acyl Chlorides with Alcohols. Norris, Banta, and Blake²⁹ investigated the rates of reaction of various substituted diphenylchloromethanes with ethyl and isopropyl alcohols. The variations in reactivity with the substituent are evident from the summary of the results given in Table XII.

TABLE XII

RELATIVE VELOCITY CONSTANTS OF THE REACTIONS BETWEEN ETHYL ALCOHOL AND CERTAIN DERIVATIVES OF DIPHENYLCHLOROMETHANE

Temperature 25.0°. Concentration of chloride approximately 0.1 formal by weight.

| Substituent | Relative Values of Constants | Substituent | Relative Values of Constants | Substituent | Relative Values of Constants |
|------------------|------------------------------|-----------------------|------------------------------|--------------------|------------------------------|
| No substituent | 1 | <i>p</i> -Methyl | 16.2 | <i>o</i> -Methoxy | 93.0 |
| <i>o</i> -Chloro | 0.01 | <i>p,p'</i> -Dichloro | 0.15 | <i>p</i> -Methoxy | 1200 (?) |
| <i>m</i> -Chloro | 0.045 | <i>p,p'</i> -Dimethyl | 413.0 | <i>p</i> -Phenoxy | 31.6 |
| <i>p</i> -Chloro | 0.42 | <i>p</i> -Ethyl | 20.9 | α -Naphthyl | 7.2 |
| <i>o</i> -Methyl | 2.9 | <i>p</i> -Bromo | 0.33 | Benzylphenyl- | |
| <i>m</i> -Methyl | 2.1 | <i>p</i> -Phenyl | 12.8 | chloromethane | 0.000 |

²⁹ Norris, Banta, and Blake, *ibid.*, **50**, 1804, 1809 (1928).

The relation between the structure of the alcohol and its rate of reaction with *p*-nitrobenzoyl chloride has been studied by Norris, Ashdown, and Cortese.³⁰ They also observed the effect of substituents in the benzoyl chloride upon the rate of reaction with isopropyl alcohol. A summary of their data is given in Tables XIII and XIV.

TABLE XIII

SECOND-ORDER VELOCITY CONSTANTS FOR THE REACTIONS BETWEEN
ALCOHOLS AND *p*-NITROBENZOYL CHLORIDE IN ETHER

Temperature, 25°. Concentration of each reactant 1 mole in 1000 g. of ether taken as unity.

| Normal Primary Alcohols | | Secondary Alcohols | |
|--|----------|------------------------|----------|
| | <i>k</i> | | <i>k</i> |
| Methanol | 0.184 | Propanol-2 | 0.0100 |
| Ethanol | 0.085 | Butanol-2 | 0.0071 |
| Propanol-1 | 0.066 | Pentanol-2 | 0.0059 |
| Butanol-1 | 0.074 | Hexanol-2 | 0.0065 |
| Pentanol-1 | 0.079 | Pentanol-3 | 0.0036 |
| Hexanol-1 | 0.085 | Heptanol-4 | 0.0027 |
| Heptanol-1 | 0.069 | | |
| | | Tertiary Alcohols | |
| Primary Alcohols with a Branched Chain | | Methyl-2-propanol-2 | 0.0027 |
| | | Methyl-2-butanol-2 | 0.0025 |
| | | Methyl-3-pentanol-3 | 0.0014 |
| | | | |
| Methyl-2-propanol-1 | 0.031 | Aromatic Alcohols | |
| Methyl-2-butanol-1 | 0.036 | | |
| Methyl-2-pentanol-1 | 0.034 | | |
| Methyl-3-butanol-1 | 0.073 | | |
| Methyl-3-pentanol-1 | 0.077 | | |
| Methyl-3-hexanol-1 | 0.075 | | |
| Methyl-4-pentanol-1 | 0.068 | | |
| | | Benzyl | 0.0170 |
| | | β -Phenylethyl | 0.0400 |
| | | γ -Phenylpropyl | 0.0200 |
| | | α -Phenylethyl | 0.0005 |
| | | α -Phenylpropyl | 0.0005 |
| | | α -Phenylbutyl | 0.0005 |

The substitution of methyl, ethyl, phenyl, α -naphthyl, methoxy, and phenoxy groups, especially in the *para*-position, enhances the reactivity of the halogen in diphenylchloromethanes. The substitution of halogens especially in the *ortho*-position reduces the reactivity of the chlorine. However, in benzoyl chlorides the halogens and especially the nitro group enhance the reactivity of the chlorine, while a methyl group lowers the reactivity.

The primary alcohols except methyl alcohol and those with a branched chain at the 2-carbon atom show a similar reactivity with *p*-nitrobenzoyl chloride. Methyl alcohol is more reactive than the

³⁰ Norris, Ashdown, and Cortese, *ibid.*, **47**, 837 (1925); **49**, 2640 (1927).

TABLE XIV

FIRST-ORDER VELOCITY CONSTANTS OF THE REACTIONS OF CERTAIN ACYL CHLORIDES WITH ISOPROPYL ALCOHOL

Temperature, 25.0°. Concentration approximately 0.1 formal per 1000 g.

| Acyl Chloride | <i>k</i> | Ratio of Constant to that of Benzoyl Chloride |
|-------------------------|----------|--|
| Benzoyl | 0.00365 | 1 |
| <i>p</i> -Chlorobenzoyl | 0.00559 | 1.53 |
| <i>p</i> -Bromobenzoyl | 0.00650 | 1.78 |
| <i>p</i> -Iodobenzoyl | 0.00528 | 1.26 |
| <i>o</i> -Nitrobenzoyl | 0.00694 | 1.90 |
| <i>p</i> -Nitrobenzoyl | 0.03600 | 10.0 |
| <i>p</i> -Methylbenzoyl | 0.00235 | 0.64 |

average primary alcohol; alcohols with carbon substituents, especially a phenyl group on the 1- or 2-carbon, are very much less reactive. The secondary and tertiary alcohols show a much lower rate of reaction than any of the primary alcohols except those having an α -phenyl group.

In later papers Norris and his associates³¹ have extended their investigations to include the rates of reaction of various substituted benzoyl halides at various temperatures and in a variety of solvents. The relative reactivity of the reactants was found to vary with all these variables. Three of their more general conclusions were as follows: It is shown that the effect of CH_3 , CH_3O , Cl , Br , I , and NO_2 in the *ortho*-, *meta*-, and *para*-positions in the benzoyl chlorides is opposite from the effect of the same substituents in the benzyl chlorides. The temperature coefficients of the reactions bear no relationship to the rates but can be correlated with the nature of the substituent and its position. The rates in solvents containing oxygen are less than in the hydrocarbons or their halogen derivatives. In this respect an acyl chloride differs from an alkyl chloride.

Rates of Reaction of Alkyl Bromides and Piperidine. McElvain and Semb³² have compared the rates of reaction of fourteen alkyl bromides with piperidine. Under the conditions of their measurements there was no appreciable amount of side reactions with the primary and a negligible amount with the secondary alkyl bromides. The rates of reaction of the tertiary bromides in alkylation cannot be compared with the primary and secondary bromides because the main reaction of the former was the loss of hydrogen bromide. The rates of the reaction

³¹ Norris, Young, Fasce, Staud, and Haines, *ibid.*, **57**, 1415-1427 (1935).

³² McElvain and Semb, *ibid.*, **53**, 690 (1931).

in petroleum ether were determined from the amounts of piperidine hydrobromide which had precipitated from the reaction mixture after a given time interval, e.g.



Among the straight-chain primary alkyl bromides only ethyl showed a marked divergence from the average of the six bromides of this type investigated. Branching of the chain (isobutyl and isoamyl) greatly lowered the rate of reaction. The phenyl group when attached to the carbon atom holding the halogen (benzyl) enormously increased reactivity. The effectiveness of the phenyl group was also manifest in phenylpropyl and to a less extent in phenylethyl. The secondary bromides, especially cyclohexyl, were very much less reactive than the other compounds investigated.

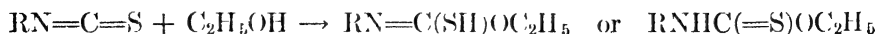
TABLE XV

RATE OF THE REACTION BETWEEN PIPERIDINE AND VARIOUS ALKYL BROMIDES AT 90°

| Alkyl Group | % Reaction in Hours | | | | |
|----------------------------|---------------------|------|------|------|------|
| | 4 | 8 | 12 | 24 | 48 |
| Ethyl | 72.2 | 80.4 | 84.3 | 93.7 | 98.4 |
| <i>n</i> -Propyl | 45.6 | 59.5 | 66.6 | 79.3 | 89.5 |
| Isopropyl | .. | .. | .. | 17.3 | 28.1 |
| <i>n</i> -Butyl | 46.1 | 59.3 | 66.5 | 78.0 | 88.4 |
| Isobutyl | 10.0 | 16.0 | .. | 29.4 | 40.8 |
| <i>sec.</i> -Butyl | .. | .. | .. | 6.7 | 12.0 |
| <i>n</i> -Amyl | 48.1 | 63.6 | 69.8 | 80.7 | 90.5 |
| Isoamyl | 31.1 | 44.8 | 52.8 | 65.5 | 77.4 |
| <i>n</i> -Hexyl | 19.6 | 63.7 | 70.7 | 80.7 | 88.9 |
| <i>n</i> -Heptyl | 53.2 | 67.5 | 74.5 | 82.2 | 90.0 |
| Cyclohexyl | .. | .. | .. | 1.1 | 2.4 |
| Benzyl | 100.5 ⁴ | .. | .. | .. | .. |
| Phenylethyl | 59.6 | 69.5 | 77.1 | 90.6 | 95.0 |
| Phenylpropyl | 74.0 | 83.9 | 86.4 | 93.2 | 95.8 |

⁴ 97.9 per cent in 2 hours

Rates of Formation of Thiourethanes. Browne and Dyson³³ have carried out a very comprehensive series of experiments upon the rate of reaction of arylthiocarbimides with ethyl alcohol. They found that this reaction proceeded at a measurable rate with a wide variety of



³³ Browne and Dyson, *J. Chem. Soc.*, 3285 (1931).

thiocarbimides. The reaction was irreversible and comparatively free of side reactions, and it proceeded in the liquid phase without the separation of a solid. The reaction was carried out by refluxing the thiocarbimide in a 100 to 150 molecular excess of ethanol. The rate of reaction was not sensitive to hydrogen-ion concentration. The reaction could be followed by an accurate analytical method which involved weighing the thiocarbimides formed by the reaction of benzidine with residual arylthiocarbimide. The values of the rate constant calculated for a monomolecular reaction are summarized in Table XVI.

TABLE XVI

| Thiocarbimide | $k \times 10^4$ | Thiocarbimide | $k \times 10^4$ |
|----------------------------|-----------------|--------------------------------|-----------------|
| Phenyl | 0.52 | 3-Chloro-4-methylphenyl | 2.08 |
| 2-Tolyl | 0.14 | 3-Chloro-2-methylphenyl | 0.68 |
| 3-Tolyl | 0.39 | 3-Chloro-1,6-dimethylphenyl | 0.41 |
| 4-Tolyl | 0.30 | 3-Chloro-2,4,6-trimethylphenyl | 0.00 |
| 2,3-Dimethylphenyl | 0.11 | 4-Chloro-2-methylphenyl | 0.44 |
| 2,4-Dimethylphenyl | 0.09 | 4-Chloro-3-methylphenyl | 1.41 |
| 2,5-Dimethylphenyl | 0.09 | 2-Chloro-5-methylphenyl | 0.95 |
| 2,6-Dimethylphenyl | 0.00 | 2-Chloro-3-methylphenyl | 0.95 |
| 3,5-Dimethylphenyl | 0.22 | 2-Chloro-4-methylphenyl | 0.78 |
| 2,4,6-Trimethylphenyl | 0.00 | 2-Chloro-6-methylphenyl | 0.28 |
| 3,4,6-Trimethylphenyl | 0.00 | 2-Bromo-4-methylphenyl | 0.00 |
| 4-Ethylphenyl | 0.26 | 2-Chloro-3,4,6-trimethylphenyl | 0.00 |
| 4-Isopropylphenyl | 0.00 | 2-Methoxyphenyl | 0.10 |
| 6-Methyl-3-isopropylphenyl | 0.00 | 3-Methoxyphenyl | 0.58 |
| 2-Chlorophenyl | 1.24 | 4-Methoxyphenyl | 0.46 |
| 2-Bromophenyl | 1.40 | 2-Ethoxyphenyl | 0.07 |
| 2-Iodophenyl | 0.00 | 3-Ethoxyphenyl | 0.75 |
| 3-Chlorophenyl | 2.99 | 4-Ethoxyphenyl | 0.27 |
| 3-Fluorophenyl | 2.88 | 2,5-Dimethoxyphenyl | 0.22 |
| 3-Bromophenyl | 3.09 | 2,6-Dimethoxyphenyl | 0.00 |
| 3-Iodophenyl | 3.31 | 3,4-Dimethoxyphenyl | 0.58 |
| 4-Fluorophenyl | 1.41 | 3,5-Dimethoxyphenyl | 0.86 |
| 4-Chlorophenyl | 2.17 | 3-Chloro-4-methoxyphenyl | 2.14 |
| 4-Iodophenyl | 2.74 | 4-Chloro-3-methoxyphenyl | 2.91 |
| 2,4-Dichlorophenyl | 4.10 | 5-Chloro-2-methoxyphenyl | 0.47 |
| 2,5-Dichlorophenyl | 4.62 | 5-Chloro-3-methoxyphenyl | 4.57 |
| 3,5-Dichlorophenyl | 17.90 | 4-Acetylphenyl | 6.84 |
| 3-Chloro-5-methylphenyl | 3.04 | 4-Biphenyl | 0.90 |
| 3-Chloro-6-methylphenyl | 0.92 | 3-Cyanophenyl | 11.10 |
| | | 4-Cyanophenyl | 4.81 |

"The results demonstrate that the nuclear substituents have a profound effect on the reactivity of the isothiocyano-group in arylthiocarbimides. Whereas halogen atoms and nitro-groups (and the methoxy- and the ethoxy-group in the *m*-position) accelerate the rate of reaction with ethyl alcohol, alkyl or *o*- and *p*-alkoxy groups retard the addition.

Any explanation of these facts must also account for the following phenomena:

"(1) The effect of more than one substituent is approximately the sum of the effects of the substituents acting alone, as e.g., in the chlorotolyl-, the chloroalkoxy-, and the dichlorophenylthiocarbimides.

"(2) The *m*-substituted compound is always more reactive than the corresponding *o*- or *p*-substituted compound. This result is independent of whether the compound reacts more readily than phenylthiocarbimide or otherwise. In this connection, the results obtained with the methoxy- and ethoxy-substituted phenylthiocarbimides are of interest, since they show that the superior reactivity of *meta*-substituted derivatives is retained even when the reactivity of unsubstituted phenylthiocarbimide lies between that of the *m*- and the *p*-substituted compound.

"(3) The reactivity varies with the nature of the substituent group¹ the nitro-group being most active in acceleration, and the isopropyl group most active in inhibition.

"(4) The anomalous behavior of the *ortho*-substituted compounds, which in some cases exhibit the usual phenomena of steric hindrance and in others do not."

Reliability of the Equilibrium and Rate Constants. It will be evident from earlier sections of this chapter that different authors prefer to express their results in different ways. It will be well to consider the merits and limitations of these different modes of expression. The simplest way of expressing the relation of structure to concentration at equilibrium is by giving the per cent conversion at equilibrium of one of the reactants. Such figures are directly related to the analytically determined concentrations, and the reader is in a position to determine whether or not a reported difference between two sets of reactants is of significant magnitude. For example, acetaldehyde under specified conditions is converted to an acetal with *n*-butanol to the extent of 96 per cent, and 99 per cent with isoamyl alcohol. If these results are expressed as equilibrium constants the value for the former is 3 and for the latter 13. Thus the difference (if any) between these alcohols is magnified. Relatively few people are able to distinguish significant differences in experimental results after these results have gone through a few mathematical transformations.

However, there are a number of reasons why it is advisable to calculate equilibrium constants. Among others it is seldom possible to make all comparisons at the same concentration of reactants so that it is necessary to calculate the equilibrium constant in order to put the results in comparable form. Further, the comparison of the equilibrium constants for the same reactants at different concentrations is one of

the best means of ascertaining whether the reaction involved is truly reversible. Two methods are used in the calculation of equilibrium constants. In the method commonly used the concentrations of reactants at equilibrium are expressed in moles per liter. This method is satisfactory if the reaction is measured in a fairly dilute solution or if there is relatively little difference between the molecular volumes of the substances whose reactivities are being compared. The second method in which the concentrations are expressed in mole fractions should be used where a series of alcohols, for example, are being compared in the absence of an added solvent, as otherwise large differences in the value of K will appear where there are no real differences in chemical reactivity. For example, two acetals having similar per cent conversion at equilibrium had equilibrium constants differing from each other by 50 per cent when the concentrations were expressed in moles per liter. In fact, the alcohol with the *higher* conversion had the *lower* value for K .

From the standpoint of theoretical chemistry, differences in structure as manifested by differences in the extent of reaction should be expressed by differences in the decrease of free energy (ΔF) for the reactions. The value of ΔF may be calculated from the equilibrium constant or from measurements of the electromotive force as by Conant and Fieser. However, if ΔF is calculated from an equilibrium constant, which is not referred to the gaseous state, then small differences cannot be considered to be significant. A quotation from Conant² is pertinent to this point. "If one should accept the cases of the quinones and the enols as typical, one might be inclined to give up all attempts to measure and correlate a series of equilibrium measurements of organic reactions. The experiments with the gas phase are time-consuming and only possible in favorable cases; the results obtained may be regarded as an abstraction without value in formulating the organic chemistry as we know it, which, after all, is the chemistry of liquid mixtures and solutions. I do not think such pessimism would be justified, however, although I do believe the results I have just considered raise serious doubts about the significance of empirical relations between structure and slight differences in free energy. If this is the case, an attempt to correlate free energy changes and molecular structure should be concerned with differences considerably greater than 1 kcal., unless the gas phase is taken as the reference state or unless there is a very good reason to believe that the disturbing intermolecular forces are weak or cancel in the measurements."

The relative rates at which compounds react may be most simply stated by plotting the per cent formation of a product against time, or by stating the amount formed after selected intervals of time. If the

reaction is (or appears to be) a mono- or bimolecular irreversible reaction, the rate constant may be readily calculated. A graphical method is more convenient if the reaction appears to be more complicated. For this purpose the data are plotted and tangents drawn at suitable points on the curve, and from the values of the tangents the rate constant may then be calculated. Rate constants offer a very convenient and concise way of expressing relative chemical reactivity. The probable significance of small differences in rate constants has been considered above in the review of the papers by Conant and Kirner. It must always be borne in mind that apparent differences between the rates of reactions of two compounds may be due to the presence of small amounts of an impurity. This possible presence of impurities having a catalytic or inhibitory effect is remindful of an historian's statement which is expressive of most human activity: "Perhaps no man can ever free himself entirely from prejudice; still it is interesting to try."

Unfortunately, rate "constants," however calculated, are all too often not "constants" but show a "trend," i.e., decrease or increase as the reaction proceeds. This may proceed from a variety of causes. The reaction may be accelerated or retarded by a product of the reaction, or a catalyst may be activated or deactivated by such a product. A catalyst may deteriorate. The analytically determined concentrations may not be the effective concentrations, etc. Many investigators have considered only a limited range of the reaction in reporting rate constants, e.g., they have based their comparisons upon the rate of transformation of the first 10 or 20 per cent of the reactants or upon some other portion of the reaction rate curve. Authors are particularly likely to disregard the latter part of the curve since "side reactions" and the influence of the accumulated reaction products are particularly malignant as the reaction slows down.

Severity of Conditions and Comparisons of Chemical Reactivity.

The methods for the comparison of chemical reactivity illustrated above, which involve either the determination of the concentrations of the reactants at equilibrium or the comparison of rates of reaction, are susceptible of precise mathematical formulation and statement. There are, however, numerous useful comparisons which can hardly be stated except in a qualitative form. These latter methods are not satisfactory from the standpoint of theoretical chemistry, yet they are repeatedly used in teaching and in research. These methods depend upon a comparison of the severity of the conditions necessary to induce a given type of reaction to occur. The results are stated in terms of the temperature, concentration of reagent, pressure, "activity" of the reagent or catalyst, etc., required to bring about a given reaction.

For example, Norris and some of his associates have measured the temperature at which various substituted malonic acids ($\text{HO}_2\text{CCHRCO}_2\text{H}$), ethers of triphenylcarbinol $(\text{C}_6\text{H}_5)_3\text{C'OR}$, and esters of triphenylacetic acid $(\text{C}_6\text{H}_5)_3\text{CCO}_2\text{R}$ begin to decompose.³⁴ Norris states, "If the ethers are arranged according to decreasing stability toward heat, the alkyl radicals fall in the order methyl, ethyl, *n*-butyl, isoamyl, β -phenylethyl, *n*-propyl, isobutyl, benzyl, isopropyl, *sec*.-butyl. This order, with one exception, is the same as that obtained as the result of the study of the lability of the oxygen bond in alcohols ($\text{H}-\text{OR}$) as measured by the velocity of the reactions between the latter and *p*-nitrobenzoyl chloride. The two independent methods based on different types of reactions lead to the same conclusion as to the effect of radicals on the lability of bonds." A similar statement holds true for the effect of R upon the temperature of decomposition of the substituted malonic acids.

Similarly, the relative stability of primary, secondary, and tertiary alcohols towards dehydration may be stated in terms of the temperature required to obtain a detectable amount of reaction. For example, under specified conditions the temperature required for the dehydration of ethyl alcohol is 50° to 60° higher than for isopropyl alcohol.³⁵ Aryl chlorides resist hydrolysis under conditions of temperature and reagent that would bring about a rapid reaction with alkyl halides. *tert*.-Butyl chloride may be completely hydrolyzed at 25° while isobutyl chloride is quite stable. Monoalkyl-acetoacetic esters are hydrolyzed at 200° by water; dialkyl-acetoacetic esters do not react at all under these conditions.³⁶

The concentration of reagent required for a given transformation is sometimes used as a means of comparison. For example, the concentration of sulfuric acid required for the absorption of alkenes is a function of the structure of the latter. A progressively less concentrated solution of sulfuric acid is required for the absorption of the series of alkenes having the skeleton structures:³⁷ $\text{C}=\text{C}$, $\text{C}-\text{C}=\text{C}$, $\text{C}-\text{C}-\text{C}=\text{C}$, $\text{C}-\text{C}=\text{C}-\text{C}$, $\text{C}-\text{C}(\text{C})=\text{C}$, $\text{C}-\text{C}(\text{C})=\text{C}-\text{C}$. Dialkyl-acetoacetic esters or

1,3-diketones may be cleaved by an amount of sodium ethoxide which is but a small fraction of that necessary for the cleavage of monosubstituted esters or diketones.³⁶

³⁴ For reference to Norris, Young, Thompson, Tucker, and Cresswell, see *J. Am. Chem. Soc.*, **56**, 423 (1934).

³⁵ Adkins and Perkins, *ibid.*, **47**, 1163 (1925).

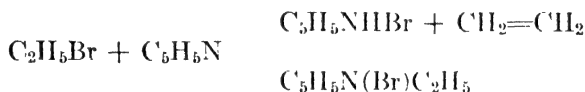
³⁶ For leading references to work of Adkins, Kutz, Connor, Wojcik, Isbell, and Beckman, see *ibid.*, **56**, 2676 (1934).

³⁷ Davis and Schuler, *ibid.*, **52**, 721 (1930).

The type or activity of a reagent (or catalyst) necessary for accomplishing a given reaction may be a useful means for the comparison of relative chemical reactivities. For example, Ziegler and Thielmann found that 40 per cent sodium amalgam did not react with tetraphenylethane while sodium-potassium alloy cleaved the hydrocarbon (p. 610).

Comparison of Chemical Reactivities on the Basis of Relative Rates of Competitive Reactions. All the above methods for the comparison of relative chemical reactivities rest on the assumption that only a single set of reaction products is formed. A more complicated situation is all too often encountered in which a comparison of chemical reactivity must be based on the relative amounts of different sets of products. Under this head come numerous comparisons of chemical reactivity. Several illustrations of these competitive reactions which have been studied for a series of compounds are given below.

Pyridine and Alkyl Bromides. Noller and Dinsmore³⁸ studied the rates of reaction of several alkyl bromides with pyridine. The two main reactions are the formation of pyridine hydrobromide and alkene and the formation of alkylpyridinium bromides, e.g.



The reactions were followed by titrating samples at suitable intervals for acidity (phenolphthalein) and for bromide (Volhard). The rates of each of the competing reactions were calculated from these data by a graphical method. The results are summarized in Table XVII.

TABLE XVII

RATES OF REACTIONS OF ALKYL BROMIDES AND PYRIDINE (118 S°)

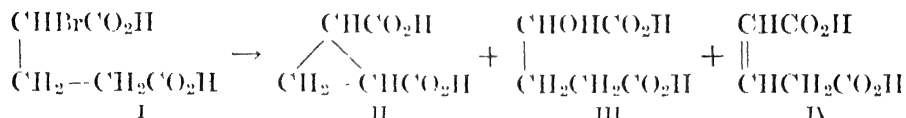
| Alkyl Bromide | Pyridine Hydrobromide | | Alkylpyridinium Bromide | |
|---------------------|-----------------------|---------------|-------------------------|---------------|
| | k_1 | Relative Rate | k_2 | Relative Rate |
| Ethyl | 0.003 | 1.5 | 0.200 | 2.1 |
| <i>n</i> -Propyl | 0.003 | 1.5 | 0.129 | 1.4 |
| Isopropyl | 0.020 | 10.0 | 0.013 | 0.14 |
| <i>n</i> -Butyl | 0.002 | 1.0 | 0.094 | 1.0 |
| Isobutyl | 0.003 | 1.5 | 0.007 | 0.07 |
| <i>sec.</i> -Butyl | 0.027 | 13.5 | 0.008 | 0.09 |
| <i>tert.</i> -Butyl | 1.75 | 875.0 | ... | ... |

These data show the greater tendency of secondary and especially tertiary bromides to lose hydrogen bromide and the slowness of the

³⁸ Noller and Dinsmore, *ibid.*, **54**, 1025 (1932).

addition of these latter halides to nitrogen. The reactivity of the four primary bromides appears to be of the same order of magnitude, the variation in relative reactivity between the extremes of *n*-butyl and ethyl bromide being as 1 to 2.

Formation of Cyclopropane Derivatives. Three major products are formed when an α -bromoglutaric acid (I) is treated with concentrated alkali, e.g., the formation of a derivative of cyclopropane (II) (p. 86), an hydroxy acid (III), and an unsaturated acid (IV).



Ingold³⁹ compared the yields of these three types of products as obtained from glutaric and two substituted glutaric acids. The yields of compounds II, III, and IV from these acids were as follows:

| | II | III | IV |
|--|-----|-----|----|
| α -Bromoglutaric | 47% | 16% | 3% |
| α -Bromo- β -methylglutaric | 64 | 8 | 9 |
| α -Bromo- β,β -dimethylglutaric | 84 | 4 | 0 |

He interpreted the larger yields of cyclopropane derivative from the α -bromo- β -methyl- and especially from the α -bromo- β,β -dimethylglutaric acids as an indication of the effect of methyl groups in increasing the stability of the cyclopropane ring.

Alkyl Halides and Silver Nitrite. The proportion of alkyl nitrites and nitroparaffins produced by the reaction of a metallic nitrite and an alkyl halide is a function of the particular metal, of the halogen, and of the alkyl group involved. A summary of the yield and proportion of isomers produced by the reaction of various alkyl iodides and bromides with silver nitrite is given in Table XVIII.⁴⁰

The results may be summarized as follows: A larger proportion of nitro compound was produced from the bromides than from the iodides with the exception of *sec*-butyl bromide. Isoamyl bromide gave more than twice as large a percentage of the nitro compound as did the isoamyl chloride. Primary halides containing a branched chain did not give as high a proportion of nitro compound as did the straight-chain compounds. If the halogen in the alkyl halide is on a secondary carbon atom, the amount of formation of the nitro compound is materially less

³⁹ Ingold, *J. Chem. Soc.*, **121**, 2676 (1922).

⁴⁰ Reynolds and Adkins, *J. Am. Chem. Soc.*, **51**, 279 (1929).

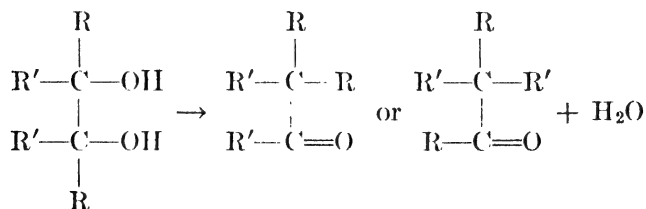
TABLE XVIII
YIELDS OF NITROPARAFFIN AND ALKYL NITRITES

| Alkyl Radical | Iodides | | Bromides | |
|---------------------|---------------------------------|------------------------------------|---------------------------------|------------------------------------|
| | Mixed Isomers Isolated, % | Nitro Compound in Mixture, % | Mixed Isomers Isolated, % | Nitro Compound in Mixture, % |
| Allyl | .. | .. | 74 | 80 |
| <i>n</i> -Propyl | 86 | 67 | 86 | 77 |
| <i>sec.</i> -Propyl | 72 | 32 | 78 | 40 |
| <i>n</i> -Butyl | 85 | 61 | 88 | 78 |
| Isobutyl | 75 | 40 | 77 | 58 |
| <i>sec.</i> -Butyl | 70 | 32 | 68 | 30 |
| <i>tert.</i> -Butyl | .. | .. | 60 | 48 |
| Isoamyl | .. | .. | 78 | 67 |
| <i>n</i> -Heptyl | .. | .. | 94 | 71 |
| <i>sec.</i> -Octyl | .. | .. | 82 | 34 |

than for the corresponding primary or tertiary alkyl halide. It cannot be said that there is, in general, either an increase or a decrease in proportion of nitro compounds with increasing molecular weight of the alkyl group. The results obtained with allyl bromide indicate that unsaturation has little or no effect on the ratio of isomers formed. The highest yields of the mixed isomers were isolated from the reaction of normal alkyl halides, the yield increasing with lengthening of the chain in the bromides.

The order of increasing rate of reaction of the alkyl halides is allyl, *tert.*-butyl, *sec.*-alkyls, isoalkyls, and *n*-alkyls. The iodides reacted more rapidly than the bromides. Butyl and isoamyl chlorides reacted more slowly than the corresponding bromides, and isoamyl chloride gave a much lower yield of the nitroparaffin than the bromide did, and even lower than the iodide of a similar alkyl radical.

Competitive Reactions in the Pinacolone Rearrangement (p. 1017). Pinacols containing two different substituents R and R' may upon rearrangement give two different ketones, depending upon whether R or R' migrates, e.g.,



The relation of the structure of R and R' to the ratio of ketones produced

has been the object of numerous investigations. The status of the problem in 1930 and 1933 is well summarized in the *Annual Reports of the Chemical Society (London)* for those years.

Bachmann ⁴¹ has extended our knowledge of the reaction in a very significant fashion which will be considered in detail. First may be considered the rearrangement of symmetrical pinacols of the type indicated in the formula above. The proportion to which various groups migrated in 24 pinacols of this type is given in Table XIX.

TABLE XIX

MIGRATION OF GROUPS IN SYMMETRICAL PINACOLS

(Results are mostly from Bachmann but include data from Montagne, Bailar, Beale, and Hatt.)

| R | % | R | % |
|-------------------------|------|----------------------|------|
| <i>p</i> -Tolyl | 94 | Phenyl | 6 |
| <i>p</i> -Tolyl | 58 | <i>p</i> -Biphenyl | 42 |
| <i>p</i> -Tolyl | 3 3 | Anisyl | 96 7 |
| <i>p</i> '-Tolyl | 90 | <i>m</i> -MeO-phenyl | 10 |
| <i>p</i> '-Tolyl | 3 | Phenetyl | 97 |
| <i>p</i> '-Tolyl | 75 | <i>p</i> -Et-phenyl | 25 |
| <i>m</i> -Tolyl | 66 | Phenyl | 34 |
| <i>m</i> -Tolyl | 13 | <i>p</i> -Biphenyl | 87 |
| <i>o</i> -Tolyl | 0 | Phenyl | 100 |
| <i>p</i> -Et-phenyl | 83 | Phenyl | 17 |
| <i>p</i> -iso-Pr-phenyl | 90 | Phenyl | 10 |
| Anisyl | 98 6 | Phenyl | 1 4 |
| Anisyl | 96 8 | <i>p</i> -Biphenyl | 3 2 |
| <i>m</i> -MeO-phenyl | 13 5 | <i>p</i> -Biphenyl | 86 5 |
| <i>o</i> -MeO-phenyl | 23 | Phenyl | 77 |
| Phenetyl | 99 | Phenyl | 1 |
| <i>p</i> -Cl-phenyl | 40 | Phenyl | 60 |
| <i>m</i> -Cl-phenyl | 0 | Phenyl | 100 |
| <i>m</i> -Cl-phenyl | 0 | <i>p</i> -Biphenyl | 100 |
| <i>o</i> -Cl-phenyl | 0 | Phenyl | 100 |
| <i>p</i> -Br-phenyl | 42 | Phenyl | 58 |
| <i>p</i> -Br-phenyl | 4 5 | <i>p</i> -Biphenyl | 95 5 |
| <i>m</i> -Br-phenyl | 0 | Phenyl | 100 |
| <i>p</i> -Br-phenyl | 0 | Phenyl | 100 |

Table XX gives the "migration aptitudes" of the various radicals (as referred to phenyl equals 1), calculated by Bachmann from the figures in Table XIX. For example, the *p*-tolyl radical migrated to the extent of 94 per cent and the phenyl to the extent of 6 per cent. The migration aptitude of *p*-tolyl is 94/6 of that of the phenyl or 15.7.

⁴¹ For leading references, see Bachmann, and Steinberger, *ibid.*, **56**, 170 (1934).

TABLE XX
MIGRATION APTITUDES IN SYMMETRICAL PINACOLS

| (Bachmann) | | | |
|---------------------------|----------|-------------------------|-----|
| Anisyl | 400 | Phenyl | 1.0 |
| Phenetyl | 400 | <i>p</i> -Iodophenyl | 1.0 |
| <i>p</i> -Tolyl | 15.7 | <i>p</i> -Bromophenyl | 0.7 |
| <i>p</i> -Biphenyl | 11.5 | <i>p</i> -Chlorophenyl | 0.7 |
| <i>p</i> -Isopropylphenyl | 9 | <i>o</i> -Methoxyphenyl | 0.3 |
| <i>p</i> -Ethylphenyl | 5 | <i>m</i> -Bromophenyl | 0 |
| <i>m</i> -Tolyl | 1.9 | <i>m</i> -Chlorophenyl | 0 |
| <i>m</i> -Methoxyphenyl | 1.6, 1.8 | <i>o</i> -Bromophenyl | 0 |
| | | <i>o</i> -Chlorophenyl | 0 |

Table XXI shows the extent to which R and R' migrated in seven pinacols not previously studied as compared with the migrations as predicted from the figures in Table XX. It is obvious that there is an extraordinarily close agreement between the ratio of products predicted and found. In other words, the "migration aptitudes" appear to be independent of the particular symmetrical aromatic pinacol involved.

TABLE XXI
COMPARISON OF PREDICTED AND ACTUAL MIGRATIONS

| (Bachmann) | | | | | |
|--------------------|----------------|------------|------------------------|----------------|------------|
| Groups | Predicted % | Found % | Groups | Predicted % | Found % |
| <i>p</i> -Tolyl | 57 | 58 | Phenetyl | 99.8 | 99 |
| <i>p</i> -Biphenyl | 43 | 42 | Phenyl | 0.2 | 1 |
| <i>m</i> -Tolyl | 14 | 13 | <i>p</i> -Bromophenyl | 6 | 4.5 |
| <i>p</i> -Biphenyl | 86 | 87 | <i>p</i> -Biphenyl | 94 | 95.5 |
| Anisyl | 97.5 | 96.8 | <i>p</i> -Ethylphenyl | 21 | 25 |
| <i>p</i> -Biphenyl | 2.5 | 3.2 | <i>p</i> -Tolyl | 76 | 75 |
| | | | <i>p</i> -Biphenyl | 100 | 100 |
| | | | <i>m</i> -Chlorophenyl | 0 | 0 |

Quite a different result was obtained when the migration aptitudes of unsymmetrical pinacols $R_2C(OH)C(OH)R'_2$ were studied, for here the relative rate of migration of R' and R is complicated by the effect of these radicals in determining whether the oxygen eliminated to form water comes from the carbon atom carrying R' or R. Table XXII gives the relative amounts of migration of various radicals in such unsymmetrical pinacols, and Table XXIII the migration aptitudes

calculated from the data in Table XXII. It will be noted that the migration aptitudes are not independent of the structure of the pinacol used as a basis of comparison.

TABLE XXII

MIGRATION OF GROUPS IN UNSYMMETRICAL PINACOLS $[R_2C(OH)C(OH)R'_2]$

(Bachmann)

| R | % | R' | % |
|---------------------|----|-----------------|----|
| Anisyl | 28 | Phenyl | 72 |
| Phenetyl | 33 | Phenyl | 67 |
| <i>p</i> -Tolyl | 49 | Phenyl | 51 |
| <i>m</i> -Tolyl | 50 | Phenyl | 50 |
| <i>p</i> -Cl-phenyl | 43 | Phenyl | 57 |
| <i>p</i> -Biphenyl | 54 | Phenyl | 46 |
| <i>p</i> -Biphenyl | 58 | <i>m</i> -Tolyl | 42 |
| Anisyl | 45 | <i>p</i> -Tolyl | 55 |
| Phenyl | 78 | Biphenylene | 22 |
| <i>m</i> -Tolyl | 54 | Biphenylene | 46 |
| <i>p</i> -Tolyl | 14 | Biphenylene | 26 |
| Anisyl | 2 | Biphenylene | 98 |
| Phenetyl | 4 | Biphenylene | 96 |

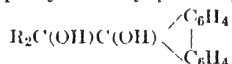
TABLE XXIII

MIGRATION APTITUDES IN UNSYMMETRICAL PINACOLS

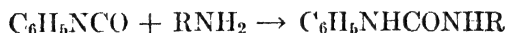
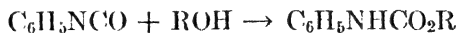
(Bachmann)

| Group | (a) | (b) |
|---------------------|------|-------|
| Anisyl | 0 39 | 0 006 |
| Phenetyl | 0 49 | 0 012 |
| <i>p</i> -Cl-phenyl | 0 75 | |
| <i>p</i> -Tolyl | 0 96 | 0 046 |
| Biphenylene | | 0 31 |
| <i>m</i> -Tolyl | 1 00 | 0 33 |
| Phenyl | 1 00 | 1 00 |
| <i>p</i> -Biphenyl | 1 18 | |

The figures in column (a) are from phenyl and tolyl pinacols; those in (b) are from pinacols containing biphenylene, e g



Competition in the Reaction of Two Alcohols or Amines with Phenyl Isocyanate. Davis, Farnum, and Ebersole⁴² have made significant studies with respect to the relative rates at which various pairs of alcohols or amines reacted with phenyl isocyanate.

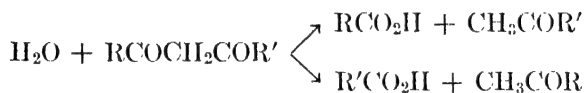


⁴² Davis, Farnum, and Ebersole, *ibid.*, **56**, 883, 885 (1934).

They allowed one equivalent of phenyl isocyanate to react with a mixture of one equivalent of each of two alcohols (or amines) and then determined the relative amounts of the two possible products.

They conclude that "the relative velocities of the primary alcohols ethyl, *n*-propyl, *n*-butyl, isobutyl, and *n*-amyl have been found to lie between 0.7 and 1.0, those of *sec*-propyl and *sec*-butyl alcohols to be about 0.33, and those of *tert*-butyl and *tert*-amyl to be less than 0.01 of the relative reaction velocity of methyl alcohol. The relative reaction velocity of aniline is about 0.5, and those of ethyl-, *n*-propyl-, *n*-butyl-, and *n*-amylamine between 8 and 10 times that of ammonia. The effect of the ethyl, *n*-propyl, *n*-butyl, and *n*-amyl groups upon the reactivity of the primary alcohols toward phenyl isocyanate is proportional to their effect upon the reactivity of the primary amines toward the same reagent."

Competition in the Cleavage of 1,3-Diketones. An unsymmetrical 1,3-diketone may cleave to give either of two sets of products, e.g.,



Bradley and Robinson⁴³ studied the hydrolysis in a 1 per cent sodium hydroxide solution of a number of diketones in which R and R' were aryl groups. A summary of their data is given in Table XXIV. They conclude that "With two exceptions the stronger of the acids which might be formed was found to be produced to the greater extent."

TABLE XXIV
CLEAVAGE OF 1,3-DIKETONES $\text{RCOCH}_2\text{COR}'$
(Bradley and Robinson)

| R | R' | RCO_2H |
|-------------------------|----------------------------|------------------------|
| Phenyl | <i>o</i> -Methoxyphenyl | 18 |
| Phenyl | <i>m</i> -Methoxyphenyl | 38 |
| Phenyl | <i>p</i> -Methoxyphenyl | 50 |
| Phenyl | <i>p</i> -Isopropoxyphenyl | 67 |
| Phenyl | <i>m</i> -Chlorophenyl | 34 |
| Phenyl | <i>p</i> -Chlorophenyl | 36 |
| Phenyl | <i>m</i> -Nitrophenyl | 18 |
| Phenyl | <i>p</i> -Nitrophenyl | 19 |
| Phenyl | 2,4-Dimethoxyphenyl | 25 |
| Phenyl | 3,4-Dimethoxyphenyl | 49 |
| Phenyl | 3,4,5-Trimethoxyphenyl | 31 |
| <i>p</i> -Methoxyphenyl | <i>m</i> -Methoxyphenyl | 21 |
| 3,4-Dimethoxyphenyl | <i>m</i> -Methoxyphenyl | 60 |
| 3,4-Dimethoxyphenyl | <i>p</i> -Methoxyphenyl | 66 |

⁴³ Bradley and Robinson, *J. Chem. Soc.*, **129**, 2356 (1926).

The alcoholysis and hydrolysis, under various conditions, of a number of aliphatic diketones have also been studied.³⁶ A summary of the data is given in Table XXV. With these compounds it does not appear that the stronger of the two possible acids (or its ester) is produced in the greater proportion. The experimental conditions during cleavage modified the ratio of cleavage products. The cleavage occurs on the unenolized side of the diketone so that the direction of enolization is an important consideration in determining the point of cleavage of the molecule.

Bartlett has written significant papers in describing his studies of competitive rates in the enolization of ketones.⁴⁴

TABLE XXV
CLEAVAGE OF UNSYMMETRICAL DIKETONES $\text{CH}_3\text{COCH}_2\text{COR}$

| R | $\text{CH}_3\text{CO}_2\text{H}$ (or Ester) % | R | $\text{CH}_3\text{CO}_2\text{H}$ (or Ester) % |
|--|---|---|---|
| <i>n</i> -C ₃ H ₇ | 43 * | <i>tert</i> .-C ₄ H ₉ | 90 * |
| <i>n</i> -C ₃ H ₇ | 49 † | <i>tert</i> .-C ₄ H ₉ | 75 § or ‡ |
| <i>n</i> -C ₃ H ₇ | 52 ‡ | <i>tert</i> .-C ₄ H ₉ | 91 * |
| <i>n</i> -C ₄ H ₉ | 54 ‡ | <i>tert</i> .-C ₄ H ₉ | 58 † |
| <i>n</i> -C ₄ H ₉ | 61 * | Furyl | 100 * |
| <i>n</i> -C ₄ H ₉ | 55 † | Furyl | 100 † |
| <i>iso</i> -C ₄ H ₉ | 66 ‡ | Cyclohexyl | 53 ‡ |
| <i>iso</i> -C ₄ H ₉ | 58 § | Cyclohexyl | 58 * |
| <i>iso</i> -C ₄ H ₉ | 65 * | Phenyl | 100 ‡ |
| <i>iso</i> -C ₄ H ₉ | 67 † | Phenyl | 80 § |
| <i>sec</i> .-C ₄ H ₉ | 81 * | Phenyl | 100 * |
| <i>sec</i> .-C ₄ H ₉ | 62 † | | |

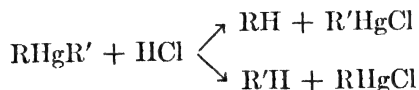
* EtOH + HCl at 60°

† One per cent aqueous solution of sodium hydroxide at 60°.

‡ Dry EtOH in brass container at 200°

§ EtOH + traces of aluminum ethoxide at 200°.

Competition in the Cleavage of Unsymmetrical Diarylmercury Compounds. Kharasch and his associates⁴⁵ have made an extensive comparison of the amounts of products obtained by the reaction of hydrogen chloride with unsymmetrical diarylmercury compounds (p. 519). The type reaction is:



⁴⁴ Bartlett and Stauffer, *J. Am. Chem. Soc.*, **57**, 2582 (1935).

⁴⁵ For leading references to work of Kharasch, Grafflin, Marker, Flenner, Sher, Reinmuth, and Mayo, see *J. Chem. Education*, **11**, 82 (1934); *J. Am. Chem. Soc.*, **54**, 674 (1932).

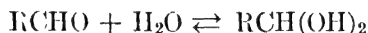
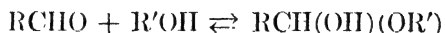
If it be assumed that the more electronegative radical unites with the hydrogen, then the relative amounts of RH and R'H formed (or of R'HgCl and RHgCl) are a measure of the relative electronegativity of R and R'. Upon this basis Kharasch has concluded that, in order of decreasing "electronegativity," certain radicals may be listed as follows: *p*-methoxyphenyl, *o*-methoxyphenyl, α -naphthyl, *o*-tolyl, *p*-tolyl, *m*-tolyl, phenyl, *p*-chlorophenyl, *o*-chlorophenyl, *m*-chlorophenyl, 2,4-dichlorophenyl, 2,5-dichlorophenyl, methyl, ethyl, *n*-propyl, *n*-butyl, *n*-heptyl, benzyl, β -phenylethyl, *p*-chlorobenzyl, *o*-chlorobenzyl, and *m*-chlorobenzyl.

Kharasch calls attention "to what to me is an extremely important and striking generalization, namely, that the electronegativity of any radical which can be made by the direct introduction of a substituent into an organic radical is lower than that of the parent substance. Thus the chlorophenyl radical is much weaker in electronegativity than the phenyl and the dichlorophenyl radical is still lower in electronegativity. The *para*-, *ortho*-, and *meta*-chlorobenzene radicals are lower in electronegativity than the benzene radical. The conclusion one would draw from these data is that whereas by superficial examination of substituted molecules one viewpoint predicts that the molecule should be more electronegative than the parent substance while the other that it should be less electronegative, the latter view would probably be true in most cases."

There is a superficial resemblance between the method for comparing radicals noted just above and, for example, Conant's method of determining the relative strength of two weak acids by allowing a molecular equivalent of each to compete for one molecular equivalent of sodium. However, there is a fundamental difference between the two methods in that the latter involves a reversible reaction while Kharasch's depends upon non-reversible reactions.

Interpretation of Data on Relative Chemical Reactivity. An important limitation upon the interpretation of data bearing upon relative chemical reactivity is that frequently the experimenter does not know exactly what he is measuring. In all studies of the variation in the concentration at equilibrium with variation in the structure of the reactants there is a strong probability that the concentrations as measured will not be the true concentrations or activities. This is true because of the prevalence of molecular association among organic compounds, especially those containing oxygen and nitrogen, which are of the most interest. Furthermore, there are few, if any, simple equilibria among organic reactions. For example, the reaction of an aldehyde with an

alcohol to form an acetal certainly involves at least three equilibria besides those concerned with the catalyst.



It is possible, of course, to measure the effective concentrations by a determination of the vapor pressures of the components of the equilibrium mixture. This has been done for a few reactants, but it is not practical to do so for an extended list. It may be that the complexity of the acetal reaction is unique, but it is equally probable that its complexity is only more apparent than that of some other reactions.

A similar situation arises with respect to rate studies, for in these the reaction measured is the slowest one involved and if several steps are concerned it is by no means certain that the slowest reaction with, let us say, benzyl chloride, is the same step in the chain as the slowest reaction with, let us say, dodecyl chloride.

A reply may be made to such criticisms to the effect that the organic chemist is not concerned with that mystic realm that never was, in which all solutions and gases are ideal, and which corresponds to a mathematician's dream. Rather is he concerned with a world of physical reality in which the solutions he uses are far from ideal, in which association and catalytic effects are coupled with a multiplicity of side reactions. The organic chemist wishes to know, first of all, something about the relative rates of reaction of various alkyl halides, for example, from whatever sources these differences may arise. Secondly, he would like to know what are the differences in molecules which result in differences in rates of reaction. Kharasch, Reinmuth, and Mayo in reference to disregarding all experiments which do not serve for the calculation of free energy changes very aptly remark: "While it is eminently safe and respectable in that it never permits one to make any mistakes, it is also eminently sterile in that it seldom permits one to do anything." And it has been said that "The notion of absolute acidity as distinct from the relative activities of some particular acid in two different solvents, must be relegated to the limbo of seductive but meaningless fiction."

Although the point of view expressed above amply justifies experimental comparison of the chemical reactivities of a series of compounds by any of the various methods, yet one should not attempt to draw conclusions from such data with a tacit assumption of ideality. Cer-

tainly one should not mix indiscriminately conclusions drawn upon the basis of equilibrium in a reversible reaction with conclusions resting upon measurements of rates of reaction or upon the severity of conditions required to accomplish a given type of transformation. These various phenomena are, of course, related, and Norris, for example, has shown a parallelism between the order of chemical reactivity of a series of substituents as measured by rates and severity of conditions required for a reaction to occur.

The facts given above with respect to rates and equilibria in the formation of semicarbazones and acetals and in the migration of double bonds show that there is no correlation between the rate of a reaction and the decrease in free energy or extent of the reaction. This, of course, is not saying that there is no connection between the rate of a reaction and thermodynamics (Chapter 23). It is merely stating that the driving force or decrease in free energy is only one of the factors determining reactions, and that in many reactions it is not a very important one in determining rates of reaction. Space factors, the *a* term in van der Waals' equation, and orienting or activating characteristics, etc., may play the determining role. The statement made above *does mean* that it is certainly unsafe to attempt to draw definite conclusions as to electronic structure (Chapter 25) on the basis of results obtained from studies of rates of reaction. In fact as Lapworth and Manske have pointed out, "It should be realized from the outset that the primary interior effect of a given substituent on an atom varies even in sign with the nature of the atom at which substitution takes place."

The interpretation of data on relative chemical reactivity based upon competitive reactions is particularly hazardous. This is true because rates of reaction and particularly relative rates of competitive reactions are so sensitive to the experimental conditions of temperature, solvent, catalyst, etc., and to apparently minor differences in the physical and chemical characteristics of the particular species of molecule undergoing reaction. Particularly striking evidence upon this point has come to light in connection with the addition of hydrogen bromide to an

alkene, i.e., $\text{RCH}=\text{CH}_2 + \text{HBr} \begin{cases} \nearrow \text{RCHBrCH}_3 \\ \searrow \text{RCH}_2\text{CH}_2\text{Br} \end{cases}$. A great many experi-

ments over a long period of time indicated that the bromine would always add to the secondary carbon as indicated in the first reaction. However, Kharasch and Mayo have shown that, with butene-1, either *sec.*-butyl or *n*-butyl bromide may be obtained depending upon whether the reaction mixture contains diphenylamine or benzoyl peroxide. Whether or not a reversal of the direction of addition is obtained de-

depends upon the solvent, the reagents, and the structure of the alkene involved.⁴⁶ Among other illustrations to the same end may be cited the following: The ratio of cleavage products of the unsymmetrical 1,3-diketones is distinctly modified by changes in the conditions of reaction (Table XXV). De Ceuster has shown the same statement to be true with respect to the cleavage of unsymmetrical simple ketones by sodium amide, sodium hydroxide, etc.⁴⁷

The ratio of alkyl nitrite and nitroparaffin produced by the reaction of an alkyl halide and silver nitrite bears little relationship to the electrochemical character of the particular alkyl group and halogen involved. The proportion of *ortho*-, *meta*-, and *para*-compounds produced by sulfonation, nitration, or halogenation of benzenoid derivatives is profoundly modified by the reagent and experimental conditions. In contrast with these reactions are the beautifully consistent results obtained by Bachmann on the relative migratory aptitudes of radicals based upon the rearrangement of symmetrical tetraaryl pinacols.

The lack of a consistent relationship between the ratio of products formed in competitive reactions and the relative stability of the products from the standpoint of energy relationship, electrochemistry, and thermodynamics is very certain. For example, it is well established that the rings in cyclic ketones (p. 105) containing six or more carbon atoms are of approximately equal stability when once formed. Yet there is a great variation in the relative yields of such ketones obtained by heating a salt of a dibasic acid, depending upon the number of carbon atoms in the chain of the acid and other factors. Ruzicka⁴⁸ has pointed out that the yield of ketone obtained is perhaps a function not only of the stability of the ring (which is constant for six or more carbon atoms) but also of the distance between the ends of the chain in the open-chain compound.*

However, the present author does not wish to suggest that the study of competitive reactions will never show the relative strength of bonds, relative electronegativity, etc., but only that such a comparison cannot be depended upon to do so. For example, Kharasch believes that the proportion of two hydrocarbons resulting from the cleavage of mercury

⁴⁶ For references see Kharasch and McNab, *J. Am. Chem. Soc.*, **57**, 2463 (1935); Sherrill, Mayer, and Walter, *ibid.*, **56**, 926, 1645 (1934); Whitmore and Homeyer, *ibid.*, **55**, 4555 (1933); Linstead and Rydon, *Nature*, **132**, 643 (1933); Ashton and Smith, *J. Chem. Soc.*, 1308 (1934); *Ann. Repts. Chem. Soc. (London)*, **36**, 219 (1939).

⁴⁷ De Ceuster, *Natuurw. Tijdschr.*, **14**, 188 (1932) [*C. A.*, **26**, 4323 (1932)].

⁴⁸ Ruzicka and co-workers, *Helv. Chim. Acta*, **9**, 512 (1926).

* It may be that the relative yields of cyclopropane derivatives obtained by Ingold, noted earlier in this chapter, are really a measure of the relative stability of the cyclopropane rings formed. Nevertheless, the method is one of dubious value.

derivatives ($R-Hg-R'$) with hydrogen chloride is independent of the experimental conditions and so serves to compare the relative "electro-negative" character of R and R' . If this be true, and the use of the tables of relative reactivities so obtained serves to rationalize a variety of experimental findings, then the method will have been of great service, for, as Kharasch remarks, "The true value of a theory or hypothesis must be determined by its utility and is in no way related to the debating prowess of its proponents."

There is no intention on the author's part of minimizing the importance of studying the relative rates of competitive reactions. Quite the contrary view is held, for apparently in no inconsiderable degree the progress of organic chemistry lies through such studies. In fact, one of the most important groups of problems in organic chemistry is concerned with the control of the ratio of competitive reactions. It is a matter of hope and of satisfaction to know that in a great many reactions the *ratio* of reaction products is not determined by the laws of thermodynamics, but that it may be modified more or less in accord with the desire of the chemist. The chemist in this field of experimentation is not like the engineer of a locomotive who must drive where the rails lead; rather is he like a man at the wheel of a car who has many roads open to him to be followed at his pleasure.

It was stated above that this chapter was not concerned with the development of "models which have properties analogous to those of the phenomena" of relative chemical reactivity. This lack of concern for hypotheses as to the mechanism of reactions, such as those of Ingold, for example,⁴⁹ should not be construed as any reflection upon the values of such hypotheses. It may be well therefore to end this chapter with another pertinent quotation from Langmuir.¹

"Skepticism in regard to an absolute meaning of words, concepts, models or mathematical theories should not prevent us from using all these abstractions in describing natural phenomena. The progress of physical chemistry was probably set back many years by the failure of the chemists to take full advantage of the atomic theory in describing the phenomena that they observed. The rejection of the atomic theory for this purpose was, I believe, based primarily upon a mistaken attempt to describe nature in some absolute manner. That is, it was thought that such concepts as energy, entropy, temperature, chemical potential, etc., represented something far more nearly absolute in character than the concept of atoms and molecules, so that nature should preferably be described in terms of the former rather than the latter. *We must now recognize, however, that all of these concepts are human inventions and*

⁴⁹ Ingold, *Chem. Rev.*, **15**, 225 (1934).

*have no absolute independent existence in nature. Our choice, therefore, cannot lie between fact and hypothesis, but only between two concepts (or between two models) which enable us to give a better or worse description of natural phenomena.** By better or worse we mean approximately simpler or more complicated, more or less convenient, more or less general. If we compare Ostwald's attempts to teach chemistry without the use of the atomic theory with a good modern course based upon the atomic theory, we get an understanding of what should be meant by better or worse."

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* Italics inserted by present author.

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